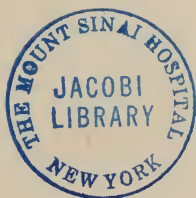




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CONTENTS

PSYCHOSOMATIC ASPECTS OF OBESITY. <i>Hilda Bruch, M.D.</i>	1
SOME CLINICAL EXPERIENCE IN THE USE OF TRIETHYLENE MEL- AMINE (T.E.M.). <i>David J. Hammerman, M.D. and Samuel</i> <i>Melamed, M.D.</i>	16
EMOTIONAL FACTORS IN THE ETIOLOGY AND THERAPY OF HYPER- THYROIDISM. <i>Theodore Lidz, M.D.</i>	27
THE INEFFECTIVENESS OF KHELLIN IN THE TREATMENT OF ANGINA PECTORIS. <i>George C. Leiner, M.D. and Simon Dack, M.D.</i>	41
THE EFFECT OF INTRANEURAL INJECTION OF BACITRACIN IN RAB- BITS. <i>Paul Teng, M.D. and Sidney W. Gross, M.D.</i>	46
PSEUDOCYST OF THE PANCREAS. <i>Alexander Richman, M.D.</i>	51
INFLAMMATORY DISEASES OF THE GASTROINTESTINAL TRACT: CLIN- ICAL CONFERENCE. <i>Frederick H. King, M.D., Alice I. Bernheim,</i> <i>M.D., Martin Sternstein, M.D., Burrill B. Crohn, M.D., Ralph</i> <i>Colp, M.D., Alvin Bakst, M.D., Samuel H. Klein, M.D., Joseph</i> <i>M. Alper, M.D., Asher Winkelstein, M.D., and David A. Dreil-</i> <i>ing, Sr., M.D.</i>	58
ABSTRACTS.....	72
BOOK REVIEW.....	87

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THE PSYCHOSOMATIC ASPECTS OF OBESITY*

HILDE BRUCH, M.D.

First of all I wish to express my appreciation for having been invited to participate in this series of lectures on recent advances in psychosomatic medicine. I feel particularly honored to have been asked to start the program with a discussion of the psychosomatic aspects of obesity. Of all the medical syndromes that have been studied from the psychological point of view, obesity is probably the one in which it is easiest to demonstrate the existence and interrelationship of somatic and psychological factors.

There is no doubt about the somatic aspect of obesity. One might say there is more "soma" than in any other condition. The very definition of obesity is that of *excessive* body weight, chiefly due to abnormal accumulation of fat tissue. Psychological factors can be recognized as being *caused* by obesity, as playing a role in its *development* and *interfering with* the seemingly simple *treatment*, namely weight reduction.

I feel somewhat uneasy that the program calls for "recent" advances. There is not much to report that can be called *recent* in the psychology of obesity. The chief concern, namely the problem of keeping slim while still eating as much as one wants, goes back to antiquity. The ancient Greeks credited the still older Cretans with having possessed the "ideal" drug that would make people slender. In spite of all scientific progress its secret has not been rediscovered and the question of how to avoid obesity is still with us. The recognition that obesity is related to neurotic problems is not new either. The opening sentence of a book called "Cursory Remarks on Corpulence: or Obesity Considered as a Disease: with a Critical Examination of Ancient and Modern Opinions Relative to its Causes and Cure", by William Wadd, surgeon, published in London, England, in 1816, reads: "If the increase of wealth and the refinement of modern times have tended to banish plague and pestilence from our cities, they have probably introduced the whole train of nervous disorders and increased the frequency of corpulence." Another clinician of the last century, Ebstein, divided obesity into three stages, known respectively as the enviable, the comical, and the pitiable.

Both these statements illustrate that the physicians of the 19th century were well aware of the socio-psychological aspects of obesity. This knowledge was lost, in a way, during the scientific era of medicine when every effort was made to explain all diseases in terms of disturbed physiology based on disordered cell function. For nearly half a century obesity research focussed on

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the discovery of some endocrine gland, the dysfunction of which was assumed to be the cause of the metabolic and nutritional changes. Consideration of the psychological aspects has become respectable again only during the last ten or fifteen years. This viewpoint was so readily accepted that one scarcely can see a second rate movie without a big fat gangster who eats all through the show and at one point or another gives a maudlin explanation that he could not help eating because something upsetting happened in his childhood. Some time ago I saw a young girl in consultation who had been unable to control her enormous weight. She spoke quite freely about the large amounts she ate. When I asked her when it first occurred to her that her overeating might have emotional causes, she looked at me in amazement and answered: "I always did. Everybody knows *that*." Such an answer stands in striking contrast to the attitude of about fifteen years ago when one had to do something approaching detective work in order to trap an overweight person into admitting that, maybe, he had not grown fat on practically no food.

The interest in and understanding of the psychological factors does not do away with the need to recognize the organic aspects of the disorder. The endocrine theories about obesity have been proven to be erroneous, at least in the naive cause-effect explanation. The weight of newer clinical and experimental evidence points to disturbances in the centers of appetite regulation in the hypothalamic region for those rare cases in which inflammatory or neoplastic changes have preceded or coincide with the development of obesity. In the great majority of so-called simple obesity no such definite localization is possible. That does not mean that somatic changes, anatomic or physiologic, will not be discovered eventually. We must admit that at present many questions about the real physiology are still unanswered. In the absence of more detailed knowledge I personally like to use the old concept of "constitution" to give recognition to the fact that there are inherent physiological factors that enter into the picture and help to explain why certain people under emotional stress resort to overeating and thereby grow fat, instead of developing other symptoms. I use the word "constitution" not in the sense of "inevitable destiny" but as a wider, more dynamic concept which identifies constitution not only with certain structural properties, such as manifest themselves in anatomic and physiologic changes, but which implies also certain dynamic qualities which express themselves in personality traits and emotional responsiveness.

A few words need to be said about the condition of overweight. The first point to be considered is that overweight people do not represent a homogeneous group. The word "overweight," as it is commonly used, indicates nothing more than a statistical term, referring to a deviation from the arithmetical mean, often called the "ideal weight." This statistical approach has been so widely accepted that most educated people know how much they "should" weigh. The concept that any deviation of more than ten percent represents "abnormality" is firmly established in medical and popular opinion.

This statistical approach denies that there are variations of body build according to which it would be normal, or natural, for certain individuals to ac-

cumulate more fat than others. It also defines as abnormal and undesirable the gradual increase of weight with advancing age, which in many people accompanies a more settled and contented adjustment to life.

In contrast to this group of people who grow heavy in accordance with their constitutional make-up there is the group of patients in whom overweight is produced by compulsive eating and is an expression of emotional maladjustment. The histories of such people are characterized by rapid increases in weight, fluctuating with changes in life adjustment. As long as the maladjustment persists there is a continuous increase in weight although eventually a plateau will be reached which is very much in excess of the average. In most of such people the potential for becoming obese pre-existed in the constitutional make-up.

There is one factor which all overweight people have in common, namely, that they are faced by medical disapproval and severe cultural condemnation. It is hard to overestimate the intensity of the cultural rejection of even mild forms of overweight, particularly in the well-to-do urban population. Most physicians condone this attitude which praises slimness as a goal in itself, justifying it by the statistically low correlation between overweight and life expectancy. In this medical attitude a condemning moralistic undertone is seldom missing. A variation of an old saying is justified, that in our society "Slenderness is next to Godliness".

This complete rejection of any degree of overweight is of particular traumatic significance during adolescence. A certain weight excess during puberty is not uncommon and is normal. Many mildly overweight adolescents, particularly girls, are forced into a serious maladjustment due to the punitive and rejecting attitude with which they are attacked by parents and age peers alike. Thus they may become secondarily abnormally obese. This course of events does not apply to all cases of obesity.

In discussing the psychological aspects, I wish to focus on the personality problems that become apparent in the process of reducing. The fact that treatment of obesity, seemingly so simple as a physiological problem, is in reality quite unpredictable due to the notoriously poor cooperation of the obese, has remained a baffling question. An understanding of the problems of reducing is of importance because one might say *reducing* has become something of an all-American preoccupation. It is no longer solely a common medical concern; it has also become "big business", the object of commercial exploitation. I am referring here to the sales value of a "new" reducing diet for newspapers or magazines, or, in more concrete form, to the practices of beauty salons and other slenderizing institutions. Physicians are well aware of the difficulty which many patients encounter in their efforts to reduce their weight. Commercial enterprises, on the other hand, promise invariable success thereby often seducing seriously disturbed obese people into senseless or even dangerous reducing procedures.

The two groups which were previously defined show a marked difference in the way they approach the question of reducing. The fairly well-adjusted overweight person is motivated by the rational goal of wanting to lose weight for

realistic reasons, commonly out of consideration for health or appearance. Without being a slave to fashion, an adequately adjusted person conforms more or less to the style of his time. For those with a natural tendency to gain weight this is a difficult task. Many of you might agree with the bon mot "Being witty is like being slim—it's beastly hard work" (Clemence Dane).

It is possible to keep one's weight down by following certain self-imposed limitations. Once overweight has developed, this is rarely sufficient. It is only the exceptionally well-integrated person, or the very obsessive one, who can follow his own dietary prescription. The majority of overweight people, even those with only a mild degree, and with good knowledge of dietetics, do much better if a definite routine is prescribed for them. It is easier to give up one's accustomed way of eating by substituting the rational authority of another person for the privilege of exercising a freedom of choice, which in this case means continuous self-denial. The great appeal of reducing fads may be explained by the fact that most people are more ready to accept an extraordinary situation than just a slight voluntary change of an established habit.

The problems of reducing for obese people are different not only in degree but also in quality. Although outwardly the goal appears to be the same, namely, that of losing weight, the inner meaning is of an entirely different nature. Reducing to the obese person is not the simple physiologic fact of losing weight, but it becomes the magical key opening the doors to the fulfillment of fantastic hopes and daydreams. It is a pathetic paradox to listen to a fat person, grossly distorted in his physique and handicapped at every turn by his appearance, discuss his future in terms of "—If I were thin," or, "—After I reduce". There is an implication that "Life" will begin only after the excess fat has disappeared. The tragic aspect is his utter inability to achieve this goal and the megalomaniac proportions of what he feels are his potential accomplishments.

A clue to this paradox is found in the symbolic meaning of the two outstanding symptoms, overeating and exaggerated bodily size. Though closely related, their meaning is not identical. The yearning for "greatness" appears to be the more basic disturbance. The psychoanalysis of obese patients reveals a grave distortion of their sense of reality. A common trait is the feeling of being "special," of "being (or having to be) bigger and better than anybody else". Obese patients feel that they had been expected to compensate for the frustrations and unfulfilled ambitions of their parents. This demand leads to a fantastic misinterpretation of their importance in the world. Such a concept is common as a passing phase in early development and is encountered to some degree in many neurotic patients. However, in the fat person this megalomaniac image of himself persists and it becomes more firmly established as it blends with seemingly realistic goals. He accepts it with the same certainty with which a schizophrenic accepts his delusions. Underlying this need of being recognized as superior to anybody else is a desperate fear of nothingness, of having no identity at all if not reaffirmed by continued admiration and praise.

As a group, fat children and adolescents are unusually gifted intellectually

and many show great artistic talent. Yet very few fulfill the promise of their early achievement. They turn continuously to new fields of endeavor only to give up as soon as they score a success. Nothing they ever achieve can come up to the exaggerated image of what they feel they could do, or are expected to do. The very fact that continued success in a field implies effort and work, something ordinary human beings have to expend, runs contrary to the fat person's concept of his specialness, of "this tremendous potential that just has to be recognized in order to fulfill itself".

To give an example: A sixteen year old, very obese boy came for psychiatric treatment because he did not want to finish high school and had become so slack in his work that there was danger of failing in spite of his excellent intelligence. His general attitude towards life was one of complete resignation. There was no sense in planning for the future, or in trying to achieve anything. His feeling about treatment was just as lackadaisical: something his parents wanted him to go through, but there was no hope and future for him. But one day he gave up his usual restraint and answered the question "What would be worthwhile?" with a passionate outburst - "What is the sense of doing homework? If you can't get 90 or 100 in all subjects, why try to do anything! Just to be average, just to be good, just to do what everybody else does - there is no sense to living that way. And even if I go on studying, who will guarantee that my name will be remembered five hundred years from now? Why should I work and exert myself just to be an average lawyer, doctor or business man. I cannot see the sense to that." This outburst of secret unrealistic ambitions in this extremely passive and pathetic boy came as a surprise to me even though I had learned about such overambitious daydreams from many other fat people.

The gulf between the aspiration level which is impossibly high and the person's inability to live up to his ambition is so great that he has to resort to some means of alleviating the tension and despair. In fat people *overeating is the most important means of relieving the felt dissatisfaction*. It fulfills the primitive hope that eating will make up for the defect. Yet, however much food they take, eating never gives the satisfaction they really want to feel; it does not accomplish the very special things they want to accomplish. The resulting increase in size fulfills on a primitive symbolic level the desire to be big. Another boy expressed it as "I'm just not big enough for what I'm cut out to do," then he stopped at the word "big" and added - "I mean in my mind - just look at me - I certainly do *look* big enough."

It is unavoidable that with such an attitude a person suffers one defeat after another and lives in an atmosphere of frustration and anxiety. In the face of all these failures and disappointments the fat person seeks comfort and solace in overeating. The invariable result of such craving is increased obesity. The social contempt for obesity is so widespread that it in turn is blamed as the cause of all the failures.

As a participant of his society a fat person shares the cultural contempt for obesity. He suffers from deep-seated disgust and self-hatred, feeling guilty for being weak and greedy. The dreams of greatness and success become now

associated with the condition of being thin. Many fat people experience a definite feeling of duality, of being two people, a fat and thin one. The socially approved and applauded thin person feels walled off and held in bondage by the contemptible greed of the fat self.

A modern writer, Connally, expresses the fat person's inner awareness of the fact that he is unable to make use of his creative potentialities, by saying, "Imprisoned in every fat man a thin one is wildly signaling to be let out." This expresses an essential aspect of the obesity problem. The question remains as to why the thin self does not succeed in breaking out of his prison. My answer would be that he does not dare to come forth because he would be expected to fulfill all these magnificent dreams of unheard-of achievement, and he dreads the possibility of failure, and this possibility is great in view of the unrealistic expectations. In this dilemma of uncertainty the "fat" personality wins out and the large physical size provides at least a symbolic semblance of being big and strong.

Once the fat person decides on reducing, or is persuaded into trying it, he approaches it with the same "all or nothing" attitude that characterizes his other unrealistic goals. The cautious calculations which a physician may offer are far below his plan of achieving slimness in a much shorter time and more dramatic way. The unabashed and unscrupulous advertising claims of the commercial enterprises promise results in keeping with the fat person's hopes, guaranteeing by their very names, Glamor, Charm and Success. These seductive promises of quick and easy transformation tally with the fat person's conception of reducing as one more expression of his special power. Even after many failures and suffering from a fatalistic sense of helplessness, the fat person thinks in the back of his mind "If I only put my will to work I can have the body I want—I can be thin any time I choose". Many seem to suffer real fear that by actually reducing this *potential of special power* will be taken away from them.

The road to slimness is beset with many obstacles. The fat person invariably encounters them in ordinary social living. Practically all social functions, and particularly those with emotional significance, are associated with lavish consumption of food and drinks which are not included in the drab routine of a reducing diet.

Obesity has become so much an object of ridicule and contempt that the social attitude toward reducing is also punitive. Many an overweight person will discover that his friends seem to be as much amused over his efforts at dieting as they were previously over his gluttony. Everybody is ready to offer advice, be it a new diet or special pills, or a warning against the dangers of losing too much weight. It has been said that there is no fool so foolish but he is an expert on obesity. I know of one physician who advises his obese patients to say that they are on an "arthritis diet" so that they could follow it without interference.

Just as an example of a rather forbidding social attitude I should like to quote the experience of a young girl at a boarding school. She was markedly overweight and the family had arranged that she receive a diet which at least

prevented further gain in weight. This girl, like so many other obese people, was excessively sensitive about anybody knowing the actual figure of her weight. Nevertheless the school made the rule that nobody could have a special diet unless her weight was checked every week. This in itself was not a bad idea; however, it was the habit of the dietician to shout out the figure so that everybody would know her exact weight, much to the embarrassment of the girl. She therefore refused to be weighed, with the consequence that in view of her "poor cooperation" she could not continue the special diet. The girl's dilemma was either to suffer the humiliation of having her weight made public, and it was above two hundred, or to eat the general starchy diet which would lead to further increase in weight.

In the case of obese children and adolescents it is usually the family who undertake the responsibility for their dieting. I assume there must be many chubby youngsters who, because of tactful handling of this problem, have been prevented from developing a more serious degree of overweight. In those obese children whose condition has persisted over a period, or has become progressively worse, the diet often becomes the focus of family arguments and such youngsters may develop an attitude of defiant resistance against the very word "diet". There are children who do not remember ever having had a meal with which they felt satisfied. They gradually developed a feeling of being looked upon "just as a body" and they expressed their bitterness in self-defeating negativism. Instead of curtailing their food intake, many obese adolescents will eat huge quantities in order to prove their independence and to show that nobody can tell them what to eat and what not to eat. It is fighting back against "this horrible life where the holes on your plate are more important than what is on it and with somebody breathing down your neck with every bite you eat". Many retain this attitude throughout adult life and the fact of "having to go on a diet" or "being told what to eat" arouses the old adolescent rebelliousness. This stubborn negativism is not limited to the attitude towards food; passive resistance is a character trait of many obese people.

Staying fat may also imply, on the interpersonal level, a continuous plea for love. Somebody who really cared for him would love him regardless of whether he were fat or thin.

More important even than these factors, are the psychological problems that go on *within* the fat person when he tries to lose weight. The whole problem becomes a conflict in power operation. A struggle may have been going on for a long time between the desire to be thin and the wish to retain the potential power which being fat implies. Fat people will follow the reducing regime in a most rigid ritualistic way. Some experience a real elation, an exaggerated sense of well-being during the early phase of reducing. The dwindling pounds and inches are proof of the effectiveness of their secret power. If the distortion of the sense of reality is severe, they may go on with reducing to the bitter end. The picture of anorexia nervosa is a tragic, though fortunately rare, outcome of reducing cures which are carried out without regard for the underlying psychological problems.

Throughout the process an inner debate goes on whether or not to continue the diet. The physical discomfort of being hungry may be too much for some; others want to feel the sensation of being hungry—"it proves that it is doing some good". The more wearing struggle, however, is between the "reducing self" and the "non-agreeing" part. A split in the personality, previously only implied, may become manifest. The reducing self tries to appease the other part by new rituals of self-indulgence, like compulsive smoking, reading of glamor magazines, or relaxing of other duties. Some live with a constant feeling of "being in danger," finding it equally as threatening to continue the diet as to break it. A deep-seated anxiety about losing body substance is often stirred up.

ILLUSTRATIVE CASES

Case 1: The patient, an obese adolescent girl, attempted reducing during her analysis. She had been a rather poor eater until she was twelve years old when she went to camp for the first time and discovered that "eating could be fun" and she indulged in all kinds of new foods. In her home meals had been served with utmost frugality. There had been always more than enough but to eat more than what was absolutely necessary was just not done. Emancipation from home became identical with the idea of "abundance", namely, eating as much as one wanted of things that thus far were doled out meagerly, such as cake and candy. There was a rapid gain in weight and she weighed nearly 200 pounds when she was fourteen years old.

The next years at home were a continuous struggle about diet. At times she might lose some weight but it would always rise as soon as she escaped the strictest supervision. She was away most of the time at boarding school. There, too, was continuous criticism of her eating habits. She was a brilliant student with enormous capacity for work—a driving compulsion to master any subject, "devouring" books and knowledge. Social relations, however, were poor and there were often repeated fights whether or not she should attend the school dances. She refused because she felt awkward and fat. There were periods of depression and great loneliness. One summer vacation had been spent at one of the reducing salons. She had accepted this in the spirit of defiance and resentment; she would show that she could do it and she lost thirty pounds or more during this experience, which she considered as the most unhappy period of her life. She gained little or no satisfaction from the fact that she was losing weight. She regained this weight in brief order. By the time she had finished high school she was in such a state of confusion and depression that she was hospitalized for the summer months, after arrangements for analysis had been made. No definite diagnosis was established except that one was dealing with a severe obsessive neurosis with marked schizoid features. The prognosis was given as guarded.

Treatment of this girl was characterized by extreme negativism, suspiciousness and aloofness. The mere mentioning of her eating habits, or of any other practical aspects of her living, would provoke deepest resentment and depression. It gradually evolved that she had a concept of life that everything and anything that had ever occurred had been forced upon her. At the same time there were frequent hints that she was engaged in more rewarding and satisfying daydreams. However, she would not divulge the content of her phantasies. She might say as much as "There are so many of us", or "Oh we know how to amuse ourselves". At times the picture resembled that of depersonalization, without awareness of a true identity. She suffered also from doubts about the reality of the people around her.

There was slow progress in her concept of reality. During the second year of treatment she enrolled in college and again mastered the academic subjects with great success complaining at the same time that there was no sense to her studying, that everything was forced upon her. The subjects of her weight and dieting were strictly avoided, yet there

seemed to be no increase in weight during the treatment period, although she had gained continuously during the preceding years.

The episode under consideration occurred in the middle of the second year of treatment. She had seen the play, "The Cocktail Party," by Eliot, and was greatly aroused by the concept of psychiatry it represented. She was enraged that the psychiatrist in the play told people what to do, that he made "choices" for them. In her own life there had been a continuous conflict between "choice" and "duty". *Duty* she defined as something one *has to do* because it involves other people. *Choice* is what one does for one's own sake alone. Her continuous complaints about being forced to do things were revolts against this excessive sense of duty.

Returning from the theatre she saw a beggar in the street and felt guilty because she walked by. Then it occurred to her that she would have felt just as guilty had she given him some money because, in a way, nothing would have been changed. She realized that this continued sense of guilt, this overwhelming feeling of what she ought to do, was an expression of the image she had of herself, namely, that she had gigantic power. It was her duty, more than anybody else's, to correct the ills of the world because she had this gigantic power. Her passivity, her just sitting by, continuously led to a sense of frustration, something she had expressed often enough—that of "not being big enough for what I was cut out to be".

She related this sense of her enormous responsibility to her childhood experiences. Instead of not having been loved enough, as many of the popular theories on neurosis try to explain, she felt that she had been loved much too much, that she had been the center of all her parents' attention. The peculiar structure of this family makes this understandable. They lived on a large country estate, as the aristocrats in a simple village; she grew up without companions who were her equals. The family did not have an active social life and they were centered on each other. She felt she received a tremendous amount of love and admiration. This was coupled with the expectation that she would make up to her parents for their own frustrations and losses, which meant that she should make up to her mother for the fact that she had not been the beauty she had wanted to be as a young girl, and to her father, (a political refugee), for the fact that he had lost his former high social position and vast possessions.

This girl had grown up in such isolation and loneliness that she had no experiences that forced her to change these basic ideas of her tremendous responsibility. She felt horrified about a possible life of middle-class contentment and so-called happiness, which to her represented a denial of her extraordinary tasks and duties and also of her gigantic power. In addition she felt that there was some special, very deep understanding between her father and herself—that they alone were the aristocrats who had to perform these duties. Mother, although she was married to Father, was not related to him and therefore not involved in the same way in this aristocratic task of saving the world. She had tried, over and over, to find in religion support for her efforts at doing good, but always was disappointed.

Her reaction to this new insight was one of relief, of no longer being confronted with tasks which always had remained undone, which always had given her a sense of being too little and which had created this deep sense of inadequacy and frustration. She recognized the relationship between this inner disappointment and her eating habits and large size.

Shortly thereafter, during a brief interruption of treatment, she began reducing on her own decision. She lost more than ten pounds during two weeks. She had made this decision, or as she called it, *a choice*, in order to demonstrate to herself that she was free now of this obsession of her special tasks and bigness. Although she had begun the diet "on her own," it soon became apparent that it was only a "part" decision. The other part of her self experienced it as a "command" and rebelled. She felt as if there had been a vote and that the "absent member" was now protesting.

By the time treatment was resumed she was in a state of extreme tension. She still

followed her self-imposed diet and was worried about not being able to break it even if she wanted to. The diet interfered with her sleep because the thought of food kept her awake. She had an insane desire for all kinds of food, even those she ordinarily loathed. She felt tired and dizzy during the day time, her knees felt weak and she felt she had to watch every step, in a physical sense as well as in regard to eating. "There is a feeling of of walking right off the edge of something—a feeling of no volition." The gravest danger was that "of drifting into eating something," particularly when she did not feel very hungry. Temptation, as "an active thing," was around all the time. She consumed large quantities of tea, smoked constantly, tried escape by reading magazines, and talked to herself in an indulgent voice. At the same time she would tell herself to stay on the diet—"a command is a command—no matter where it comes from".

The result of this continuous struggle and tension was a complete deterioration of her daily activities. She was unable to do her work—and "mastering" her studies had been another aspect of her special power. She withdrew from whatever friendships and social contacts she had gradually built up. She discontinued the efforts at dieting after three weeks with awareness that the real danger was the danger of losing her hold on reality. She tried to explain her experience in an essay from which I quote a few sentences:

"How can I explain what a diet is, how can I explain any of it. They, they do not understand. How can I tell them, if I become as they are, then I will sacrifice myself to do so, and destroy what love I have for them. I must be so careful. The jealous God. I must watch where I walk, where I go, what I say, for I may destroy myself in this perilous transition from the worship of desire back to myself. To peace, the pleasing despair, the Uncare . . .

"If I build an altar to my deepest desire, what then is precious enough to be sacrificed thereon but the self desiring? . . . There is nothing too dark to be done in the soul. The shadows of reality are undone by the knowledge of the depths within, the deep rivers going back to the sea!

"In the battle between myself and what I most wish, I have won the only victory. The desire must be sacrificed to the self."

After discontinuing the diet her weight quickly returned to the former level. The panic and tension subsided within a few days.

Reducing of this type is carried out for various lengths of time, sometimes for a few days only, more commonly for approximately three or four weeks. Then the system collapses and "one single step off the diet" suffices to destroy the whole ritual. But even if a fat person succeeds in getting his weight down, there is no inner peace if he does not achieve emotional readjustment as well. Many of these "thin fat people" suffer just as much torture and tension after losing weight. The conviction of being inadequate and inwardly awkward persists. Frequently they resume overeating because the tension of being continuously food-and-weight-conscious is more than they can bear and they overeat and become fat again in a spirit of despair.

Sometimes the preoccupation with weight and appearance in such mechanically reduced people may assume delusional character. In others there is an outbreak of a frank psychosis. My remarks about the grave psychological dangers of commercial exploitation of the weight problem are based on a number of observations on young girls who became seriously disturbed or psychotic while trapped in such beauty salon reducing. These courses expose fat young people to deepest humiliation and sadistic degradation. The last vestige of self-respect is undermined by ridicule, and competitive exhibitionism is extolled as the highest goal of life. These same patients had been "uncooperative" in

previous reducing efforts and had been seduced into the glamor schools by the skillful advertising. They were trapped into going through with the routine under the combined pressure of family concern and prepaid financial arrangements. Sometimes the psychological breakdown will not occur until a short time after the goal of weight loss and New Beauty had been achieved, when in spite of all the cruel suffering and fake changes the promised and expected success does not materialize.

These observations lead to the conclusion that however undesirable and damaging obesity is, it must be approached as a symptom that serves an important function in a precarious life adjustment. Reducing should not be attempted at this stage. Symbolically obesity fulfills megalomaniac goals, but at the same time it precludes their being put to the test of reality which is bound to be disappointing. Persistence of obesity may thus become a protecting wall against a more serious mental disturbance, even psychosis.

The common approach in the treatment of obesity has been to attack the outstanding symptom, namely, the adiposity, and to find some method, be it starvation or poison, to make the excess fat disappear. If psychological factors are given due consideration the approach becomes *one of treating fat people and their problems of living*. Whether or not weight reduction should be part of the treatment program from the beginning, or at what time it should be attempted, must be evaluated in each case. Mechanical dieting, before the fat person has found a new level of emotional adjustment on a more secure basis, is not only a futile effort, leading at best to a temporary weight reduction, but it must be considered dangerous from the point of view of mental health.

I am aware that I state the problem in a form against which there are many practical objections. When a fat person comes for treatment he expects help in losing weight. He is usually unaware of the underlying psychological problems which become clear only during therapy. To the fat man his adjustment problems are due solely to his being fat. In many years of endeavor I have not yet succeeded in keeping a patient, in particular parents of a fat child, from wanting weight reduction as the first, and often as the one and only, goal of treatment if the consultation was the first serious attempt at doing something about the condition. All the patients who were willing to undergo the tedious process of psychoanalysis and to postpone reducing until they were psychologically ready, had a history of repeated periods of weight reductions, sometimes of amazing amounts. They had become "thin fat people," but their psychological problems had remained unaltered. To them it was no news that overweight was only a secondary symptom and that they needed help to find a better adjustment in life so that they could keep their weight at a normal level.

I do not wish to imply that medical and dietetic treatment of overweight is a useless procedure. As a matter of fact, the novice who attempts reducing for the first time is usually a good subject. The results are sometimes amazing, particularly in cases in which the emotional disturbance is mild or a thing of the past, and the over-eating has become a no-longer necessary habit.

An essential aspect of treatment of obese people is the need for corrective

reappraisal of the aspiration level. Only when he pursues goals that are capable of realistic fulfillment can a fat person renounce his large size and overeating and enter on a reducing program with the prospect of enduring success and better life adjustment.

Case 2: A seventeen year old girl suffered a psychotic breakdown during a period of reducing which was forced upon her after graduation from high school as preparation for college. She became tense, restless and could not sleep. She would walk for hours by herself, would grimace, take on bizarre postures, twirl around, always mumbling to herself. The symptom that was most upsetting to the parents was her habit of staring into the mirror for a long time, giggling or bursting out in a derisive laughter. The mother felt that the facial expression often expressed "repressed crying". Most of the time she was oblivious to the environment and would not respond when talked to. However, when she noticed that she was observed she would stop her bizarre behavior and give some rational explanation or pretend that nothing had been going on. She would try to control her behavior in the presence of people but the tension was so great that she would walk off several times from the dinner table and run into the bathroom "to let out her emotions". The disturbance was so severe that hospitalization seemed advisable but was refused by the family. The girl pleaded to be permitted to go to college because she felt she could not stand staying at home. She had sufficient insight to accept that she was too disturbed to go to college. Treatment was carried out, successfully, with the aid of a trained companion.

This girl was the youngest of three children, the sister and brother being five and eight years older. During her early childhood the family's economic status improved considerably so that the parents could indulge in their numerous ailments and complaints. This meant that practically her whole childhood was spent travelling from one spa or resort to another, involving constant changes of school and making of new friends. The parents considered her an unusually good child—"too good to be true"—but they felt reassured that she had fun in her own quiet way. It never occurred to them to think that she was not happy. The parents felt they did everything they could for her by always taking her along and giving her everything she wanted. As a young child she was plump which pleased her mother.

The first continuous school experience occurred after the family settled in New York. The girl was enrolled in a renowned progressive high school. During this time she developed her first behavior difficulties which were not recognized as such but glossed over by the parents, in a spirit of what they felt was "cooperation" with the child. Having been a very conscientious little girl all her life she now began to stay away from school. There were episodes of stealing things from stores or in other families. In the course of treatment the girl tried to give an explanation for this behavior. She felt that the strain of conforming to so many different teachers in the course of a day and to gap the bridge between the psychological atmosphere of the school and of her home was more than she could stand. This insight occurred at a time when it had become clear to her that her whole life had been an effort to fulfill what she felt were the requirements and just demands of life, namely, to be perfect in every respect, particularly to live up to the high ideals of her older brother. It was during these years of strenuous effort to fulfill this ideal that she became conspicuously overweight. It was unavoidable that the weight now became the center of attention as spoiling the image of goodness and perfection which the girl thus far had fulfilled. Several efforts at weight reducing were made and when she was sixteen she succeeded in forcing her weight down with the aid of large amounts of benzdrine and thyroid.

The summer of this year was spent at the beach and she was praised for her great efforts, and success, in being popular by playing tennis all day long and dating some of the boys. However, everybody came down upon her with scorn and fury because "she was going too far" with one of the boys. The brother, in particular, acted as the absolute moral judge, reproaching her that it was the most humiliating experience for any girl to permit a "soul

kiss." This seemingly successful summer, during which she was beautiful and slim, ended with the girl becoming seriously depressed and feeling very resentful against her family. A solution of the problems was sought by sending her away to boarding school, to which she agreed under the combined family pressure. Without discussion with the school she was removed for her senior year to a very rigid formalistic boarding school. She was exceedingly unhappy and wanted to leave. Again the brother used his superior moral judgment—"You wanted it, so you have to stick it out." During this year she gained an enormous amount of weight and everybody was shocked at her appearance at graduation. The family council now decided on weight reduction and sent her to one of the commercial institutions known in and around New York as milk farms. The girl's objections were overruled. It was mandatory that she should be slim so that she could be "a success" at college. It was during this period that the serious mental disturbance occurred.

She had known that the brother planned to get married to a certain girl, of whom she approved and whom she liked. Nevertheless it came as a great shock to her when one day she received a telephone call from him that the formal engagement had been announced and a wedding date set. Reducing became even more important because unless she was slim she would not be permitted to be a bride's maid at the wedding. The disturbed behavior began shortly following this news, after she had been at the milk farm for a week or two. Her first reaction to the news had been a feeling of being completely stunned and she had no memory of what actually went on in her.

In the course of treatment it became clear what an extraordinarily important role the brother had played in the girl's life. His influence had been so overwhelming and absolute because he had been her ideal of achievement and accomplishment. She felt her parents had been too old and too preoccupied with their own health to really ever listen to her; but this brother showed interest in her development. She would send him long letters pouring out her feelings, writing poetry for him and making him the hero of all her daydreams. Her goal and task in life was to live up to his expectations. Therefore any criticism from him was of such a disastrous consequence. The news of his engagement changed the basis of her relationship to him and she felt she would lose the only person who loved and admired her. Reducing now lost any positive meaning, namely, that of being admired by him for her effort; on the contrary, it assumed a negative connotation, that she was preparing herself for a wedding at which she was going to lose him.

Case 3: A young woman succeeded in reducing her weight by regurgitation after every meal. By this method she brought her weight down from 170 to 115 pounds, which she considered her ideal weight. When she came for treatment her weight was approximately 125 pounds and she was panicky with fear that she was growing fat again. Actually she was exceedingly slim and her preoccupation about fatness had a phobic character.

Although she had thus succeeded in creating a perfect figure, her adjustment to life did not only not improve, but it deteriorated to a state of being a race between eating as much as she wanted and maintaining her perfect figure. She expressed in the course of treatment that this point was very important because it was proof of her power to defy Nature. If she could eat as much as she wanted and could stay thin, then she was doing something nobody else could get away with. Whenever she gained a pound she became depressed because "her power was slipping". This preoccupation with maintaining the perfect weight is only one example of her approach to life which was experienced as a need to be continuously reassured of "complete perfection in every respect".

She was the second of three children of a financially successful and socially prominent family. From her description and from contact with the parents, one gained the impression of a compatible and stable family relationship. The two other children developed into competent, well-adjusted people. She was a happy and pretty little girl, the favorite of her father. When she was nearly four years old the younger sister was born. She and her brother were sick with otitis at about the time of confinement of her mother. The brother recovered without complications and was discharged from the hospital but she needed an operation and stayed therefore at the hospital for several weeks. When she

came home her mother was busy with the new baby, and the care of this little girl was left to a nurse. A great change of behavior occurred during this period. From having been a friendly, outgoing girl, she now became shy and clinging and was much more attached to her mother than before. However, she made a seemingly good adjustment to school; as a matter of fact, she became a leader due to her intelligence and her great prowess in athletics and other activities.

In the patient's recollection a real change in her attitude occurred when the family moved to another city and she entered a high school as a "new" student. From then on she was continuously aware that she had to work hard in every respect to be perfect. She saved diaries from that time which abound with resolutions and decisions what to do to make herself perfect. The one fact of which her parents became aware was the great enthusiasm with which she entered on new activities, all kinds of activities, only to give them up as soon as she was successful. During this time she became somewhat overweight which to her was the reason why she could not be popular with boys.

The real difficulties began when she went to college which meant in her case leaving home for the first time. She became preoccupied with the idea of being prominent and popular and worked hard, "like a politician," during the first month to be well liked and known by everybody so that she was chosen president of her dormitory. Once she had accomplished this, her interest in the other girls lagged. She was also unable to maintain her high academic record. She apparently became quite depressed, which she had to hide from everybody in order not to spoil the record of perfection. She over-ate and gained a considerable amount of weight. From now on fatness became the big problem which stood in the way of any accomplishment. She changed to a college closer to home but was as unable as before to concentrate on work. It was at this time that one of her friends introduced her to the method of regurgitation after a particularly big meal. To her it was the ideal solution of her problem and she practiced it to such an extent that she lost weight rapidly. She was very attractive and felt reassured in her attractiveness by the fact that she had numerous boy friends. As a matter of fact, during the next few years she collected a long string of young men, many of whom wanted to marry her, something to which she was ready to agree, but then her interest in the relationship stopped. Some of these engagements were formal and the family announced them. Within five years she accumulated approximately twenty broken engagements. It gradually became clear that the only thing she was interested in was to attract a man and to get his declaration of love. Then he had fulfilled his function. Her need to be reassured that she was more attractive than any other girl was appeased for a time.

The feeling of being superior and perfect needed continuous reassurance. Whenever this was not forthcoming she would go on an eating spree. Such eating "binges" would take several hours, during which she consumed gargantuan amounts of food, until her stomach would bulge. Then she would relieve herself by vomiting. When unhappy she would go on as many as three or four eating binges. The slightest disregard for her feelings, an unplanned evening, any disappointment, or the fear of not living up to somebody's expectations, were sufficient cause to provoke the need for eating. She was unable to finish her college course or to maintain any other job because she could not resist running out for an eating binge when the slightest event shook her feeling of superiority. This feeling of her superiority included world-saving ideas of doing good for all the oppressed people or of saving and elevating individuals whom she met in the course of her many activities.

She succeeded for a while to hide her condition from her parents but gradually the disturbed nature of her never finishing anything and her many meaningless activities was recognized. There were repeated attempts at psychiatric treatment, each of which was given up, for various external reasons, after four to six months. In the course of treatment with me it became gradually clear that she had used her previous therapists as tools to help her accomplish this Godlike perfection which she described as the one and only goal of her life. Whenever she felt that the therapist was not helping her enough she would find a good face-saving reason for breaking off treatment. It was only after this delusional

goal of her therapeutic efforts had been clarified that something like a valid treatment relationship could be established.

SUMMARY

The condition of overweight is generally considered to be undesirable and is the object of continuous efforts at reducing.

From a clinical point of view it is necessary to differentiate between two types of overweight: a purely constitutional type which is an expression of a variation in body build, and a symptomatic type which is an expression of emotional maladjustment and leads to severe degrees of obesity, which also requires a constitutional predisposition. Psychological factors play a role in the development of obesity. Socio-psychological problems are created by the state of obesity.

Success or failure in reducing depends, among other factors, on the meaning of weight reduction for the patient. To the adequately adjusted overweight person it is a rational task with the main goal of losing weight. Even then it is not easy and simple and many patients need support and supervision.

To the emotionally disturbed obese person weight reduction has an irrational meaning, namely, that of fulfilling exaggerated daydreams of success and achievement. For such people reducing cannot be considered a harmless procedure. If rigidly enforced it may precipitate serious mental disturbance, even psychosis. Weight reduction should be preceded by a corrective appraisal of the aspiration level.

SOME CLINICAL EXPERIENCE IN THE USE OF TRIETHYLENE MELAMINE (TEM)*

DAVID J. HAMERMAN, M.D.† AND SAMUEL MELAMED, M.D.

INTRODUCTION

Fundamental properties and therapeutic applications of the nitrogen mustards were first investigated as part of chemical warfare research during World War II (1, 2). The extensive experience that has accumulated in the use of these agents in neoplastic diseases has been reviewed by Karnofsky (3).

More recently, certain aromatic chloroethyl derivatives have been shown to have markedly inhibitory effects on certain animal tumors (4). Burchenal *et al.* (5) as well as Lewis and Crossley (6) found that 2,4,6,triethylenimino-s-triazine (triethylene melamine, fig. 1) inhibited leukemia in mice and growth of sarcomas in rats. The pharmacology of triethylene melamine (TEM) has been studied (7) and considerable clinical evidence of the effectiveness of TEM in the treatment of lymphomas and leukemias has been obtained (8, 9).

CLINICAL STUDIES

The number of patients studied was small. The cases are not reported in an attempt to compare TEM with other forms of therapy, but to present some experiences with this drug in the therapy of far advanced chronic lymphatic leukemia and in a case of polycythemia vera.

A. *Dosage.* TEM is supplied as a 5 mg. scored tablet.‡ The usual initial course we have used is 5 mg. taken with a glass of water and repeated once daily for 2-3 days. The patient should be fasting and breakfast must be withheld after administration of the pill for at least one hour. The effectiveness of therapy is followed by the clinical course and peripheral blood count. Marrow depression similar to that produced by nitrogen mustard will occur and a second course of TEM must await evidence of bone marrow regeneration. The best guide to this is a rising or at least a stabilized white count. If a satisfactory response has been obtained, hemoglobin and platelets will also rise and this too may be used to judge marrow response. Thrombocytopenia and anemia may persist in advanced cases and then will be a reflection of the disease process itself.

When a therapeutic effect has been obtained, maintenance therapy may be continued with the administration of small doses (2.5-5.0 mgs.) at carefully spaced intervals.

B. *Immediate side effects.* Two patients noted anorexia and eructation after taking the drug. No patients vomited or had diarrhea.

* From the Medical Service of Dr. Louis Leiter, Montefiore Hospital, New York City. Presented at The Mount Sinai Hospital House Staff Conference, November 1951.

† Present Address: The Mount Sinai Hospital, New York City.

‡ Dr. D. A. Karnofsky of Memorial Hospital and Dr. L. Meyer of Goldwater Memorial Hospital were kind enough to supply the TEM.

C. Results.

1) *Chronic Lymphatic Leukemia*: Early cases of chronic lymphatic leukemia treated with nitrogen mustard¹ may show lymph node shrinkage, fall in the white count, and recession of the spleen, but as Rhoads has noted "far advanced cases with severe anemia do not respond favorably to HN₂ and its use is not recommended" (10).

The patients treated with oral TEM were far advanced cases of chronic lymphatic leukemia. This was evidenced by (1) practically complete marrow replacement by lymphocytes; (2) massive lymphadenopathy and hepatosplenomegaly; (3) persistent anemia despite repeated transfusions and (4) failure to respond to radiotherapy which previously had been effective in shrinking involved lymph nodes and organs.

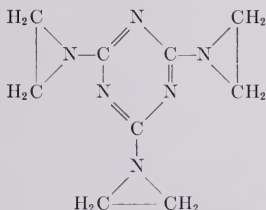


FIG. 1. Triethylene Melamine (TEM)

Case 1 (A. C. No. 50766, fig. 2) This 48 year old white man had chronic lymphatic leukemia for six years and had received radiotherapy, two courses of urethane, seven injections of P³² and at least 170 blood transfusions. The patient was icteric and had massive lymphadenopathy and hepatosplenomegaly. Further transfusions failed to raise his hemoglobin and increased his jaundice. A direct positive Coombs test was found, but circulating antibodies could not be found using saline, trypsin and albumin solutions. Bone marrow aspiration revealed extensive lymphocytic infiltration with minimal erythroid activity. Peripheral blood smears revealed mature and immature lymphocytes and no reticulocyte response. Chest X-ray revealed large mediastinal nodes and there were symptoms of compression of the trachea and superior vena cava. There was also clinical evidence of congestive heart failure. The patient received 5 mg. of TEM for two days and then after one day's lapse, a further 5 mg. were administered. Despite the rapid progression of icterus, the patient felt subjectively much improved, ate well and noted marked shrinkage of all palpable nodes and recession of the abdominal distention. The mediastinal compression was relieved. Serum bilirubin gradually fell to previous levels. Two week after initial therapy 5 mg. more of TEM were given with a marked fall in the white cell count, and further shrinkage of lymph nodes. An exacerbation of the icterus did not occur. Despite clinical improvement, transfusions were still not effective in raising the hemoglobin. Subsequently, the white cell count rose, the lymph nodes returned to their original size and the patient died a little over seven weeks after the initial TEM therapy.

Comment: In this patient with far advanced chronic lymphatic leukemia, TEM proved to be an effective agent in temporarily shrinking lymphoid tissue. Mediastinal structures were compressed by large masses of nodes and there was

marked peripheral lymphadenopathy and hepatosplenomegaly. Because of the dissatisfaction with the use of nitrogen mustard in these cases, 15 mg. of TEM were given over a four day period. Symptoms of mediastinal compression were relieved within a few days, and peripheral nodes were markedly reduced in size. Reduction in the size of the liver and spleen occurred to a lesser extent.

Icterus was noted during the administration of TEM and this drug may have been responsible for further liver damage in a patient with considerable hepatic insufficiency.

It was our impression that this patient had an acquired hemolytic anemia. Evidence for this, and a study of the effects of TEM in this condition will be discussed later.

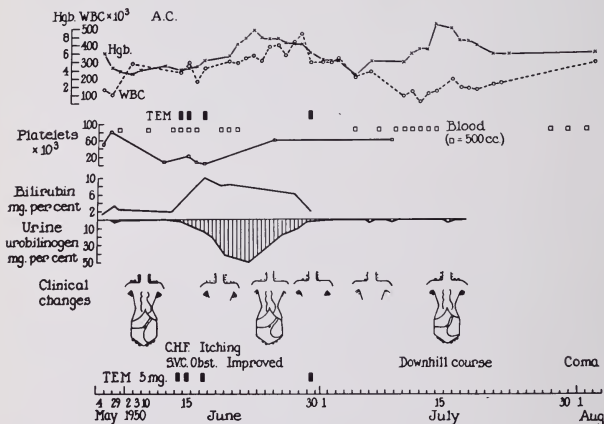


FIG. 2. Clinical course of Case 1. (A. C.)

Case 2 (No. 50779 fig. 3) This patient is a 44 year old white male who has had chronic lymphatic leukemia for seven years. He received intermittent X-ray therapy until two years before admission when he was first noted to be anemic. Since then he has received over 120 blood transfusions and five P^{32} injections but has steadily gotten worse. On examination the patient was febrile, and cachectic. There was massive lymphadenopathy, hepatosplenomegaly, and many huge intraabdominal masses. A purpuric eruption was noted over the legs. The bone marrow was extensively infiltrated with mature and immature lymphocytes. Despite many transfusions, the anemia and thrombocytopenia persisted. The patient ate poorly, lost weight, and had such marked abdominal distension that he could not turn on his side. 15 mg. of TEM were administered as an initial course followed in three weeks by an additional 10 mg. There was shrinkage of the lymph nodes and a sustained rise in hemoglobin. The patient left the hospital and received maintenance therapy of 2.5 mg. of TEM every month. There are no palpable lymph nodes, and the spleen is much smaller. The abdominal masses have been so reduced in size that the patient can move about freely and is ambulatory. His state of nutrition is fairly good. Although his

bone marrow has not shown any change, there has been a steady rise in platelets and no new purpuric spots have appeared. He has not received a transfusion in five months, and the hemoglobin has remained at about 10.5 gm.

Comment: This patient had large lymphatic masses which no longer responded to radiotherapy, and a marked anemia thrombocytopenia, and purpura over the legs. He was receiving four to six packed-cell transfusions a month without a satisfactory rise in hemoglobin. Maintenance therapy with TEM (1) brought about shrinkage of lymph nodes; (2) diminished moderately the size of the intra-abdominal masses and the spleen; (3) induced a leucopenia but did not depress the platelet count; (4) elevated and maintained the hemoglobin removing the need for transfusions during a five month period; and (5) improved the

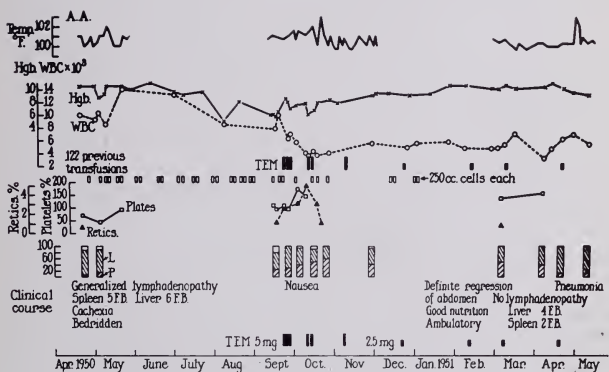


FIG. 3. Clinical course of Case 2. (A. A.)

patient's appetite and sense of well-being. Nevertheless, this patient has still extensive, far-advanced disease. His bone marrow has not been significantly altered. Moreover, follow-up reveals that despite a drug-induced leucopenia, there is a steady rise in the number of lymphocytes with the appearance of more immature forms in the peripheral blood and marrow.

A word of caution should be added regarding maintenance therapy. In one case we studied, a diagnosis of chronic lymphatic leukemia was made two years after a splenectomy for pancytopenia. This patient was treated with TEM because of marked hepatomegaly and a white count that rose as high as 100,000 with 98% lymphocytes, although subjectively she felt well and had no complaints except for moderate weakness. 37.5 mg. of TEM were given periodically over a month. With each successive course, and despite the fact that the white count was rising again, there occurred a progressively more precipitous drop in the white count (table 1). This may indicate some form of cumulative effect or a

change in the sensitivity of surviving or newly produced white cells to further TEM therapy. In the use of intravenous nitrogen mustards, Spurr et al. (11) found that when cumulative doses reached 200-650 mg. the "hemopoietic system may show a greater sensitivity to the drug after prolonged treatment."

2) *Polycythemia Vera*: Nitrogen mustard has been used to control polycythemia vera, a disease in which there is stimulation of all marrow elements. Jacobson (12) produced a remission in one patient for eighteen months and remissions in four others up to six months at the time of his report. Shullenberger et al. (13) reported remissions in four patients from two to thirteen months and found a relapse in two patients within two to three months after mustard therapy. Bauer and Erf (14) felt that nitrogen mustard is inferior to P³² in the treatment of polycythemia vera. They noted that there is danger of intracranial bleeding if excessive vomiting occurs following mustard therapy.

TABLE I

WBC BEFORE NEXT TEM COURSE	TEM MG. CUMULATIVE DOSE	LOWEST WBC AFTER TEM
70,000	0	—
70,000	12.5	47,000
63,000	17.5	48,000
61,000	27.5	38,000
59,000	37.5	6,350

Since, in our cases TEM did not produce vomiting, and could be easily administered to ambulatory patients, it seemed worthy of trial in polycythemia vera.

Case 3 (S. F. No. 52514, fig. 4). The patient is a 56 year old white furrier who has had mild essential hypertension for three years. Four months before admission to Montefiore Hospital the patient noted dizziness, giddiness, headaches, some blurring of vision and weakness. A blood count was said to show an elevated hemoglobin and red count.

Examination revealed a markedly plethoric man. The BP was 184/108. There was injection of the conjunctiva and scleral vessels and fullness of the retinal veins. The heart was normal. The liver and spleen were slightly enlarged.

Laboratory data revealed a hemoglobin of 27 Gm., a red cell count of 7.15 million, a white cell count of 10,000 with a normal differential, a platelet count of 812,000 with a bleeding time of 2½ minutes and a clotting time of 6 minutes. Reticulocyte count was 0.8% hematocrit 73% and uric acid 7.2 mg. %. The sedimentation rate was 0 in one hour. Two BMR's were +3 and +8. Bone marrow was markedly hyperplastic with erythroblastic hyperplasia, and a marked increase in megakaryocytes. With the use of Evans blue dye T-1824, the plasma volume was found to be 3750 cc. and the total blood volume 13,914 cc. (Expected normal blood volume = 5467 cc.)

The patient was given 10 mg. of TEM and then approximately monthly doses of 5 mg. of TEM. After 25 mg. a steady fall in hemoglobin was induced. At no time was a severe leucopenia noted, the white count not falling below 4800 although a marked lymphopenia occurred. Two months after institution of therapy, the hemoglobin was 15 Gm. and the white count 7000. The patient was followed in the Out Patient Department and about 3½ months after starting therapy, he had a slight return of symptoms with a rise of hemoglobin to 21 Gms. 5 mg. more of TEM were given. Follow up revealed that the hemoglobin had fallen to 13 Gms., the white count to 6500, and the platelet count to 370,000. The hematocrit was 51% and the blood volume 7500 cc. The spleen was still palpable and the blood pressure unchanged. Maintenance TEM therapy has kept up the desired effect of sustained bone marrow suppression, and the patient is asymptomatic.

Comment: Because of oral administration and absence of immediate side effects, TEM would seem to be more advantageous than nitrogen mustard in the therapy of polycythemia vera. That the hemoglobin can be brought to normal levels and yet the white count maintained on fairly large doses of TEM is evident from this case. The drug may be kept up in maintenance form and easily administered periodically to out-patients.

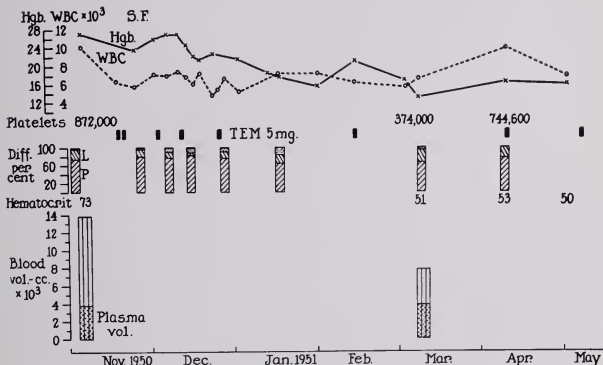


FIG. 4. Clinical course of Case 3. (S. F.)

DISCUSSION

This paper has presented clinical studies of the use of an oral drug with nitrogen mustard-like action—triethylene melamine—in the treatment of chronic lymphatic leukemia, and polycythemia vera. Only a small number of cases were studied and no attempt was made to compare results of oral TEM administration with other forms of therapy now in use. Furthermore, in this series, only the patient with polycythemia vera had not received previous treatment. The other patients had far advanced malignant disease, and had received most of the available forms of therapy prior to TEM administration.

A. Chronic Lymphatic Leukemia: In far advanced chronic lymphatic leukemia, nitrogen mustard has been unsatisfactory. Initial experience with TEM by Rhoads et al. (8) showed that in this disease lymphatic tissue appears to be quite sensitive to the effects of TEM. In our patients, shrinkage of lymph nodes, liver, spleen, and intra-abdominal masses occurred after TEM therapy, even when these organs had failed to recede with previous X-ray therapy. It should be emphasized, however, that reduction in size of involved organs is neither complete nor permanent, and that bone marrow aspirations showed persistent lymphocytic infiltration. Our cases had subjective improvement following TEM administration similar to that often noted in far advanced Hodgkin's disease after the use of intravenous mustard, namely, an increased appetite, a feeling of

well being, and new strength that may convert a bed-ridden patient into an ambulatory one.

1. Hemolytic Syndrome. Hemolysis in the course of malignant disease is well known. Dameshek and Schwartz (15) classified these cases as "symptomatic acquired hemolytic anemia". Hemolysis may occur during the course of lymphosarcoma, Hodgkin's disease (16) and chronic lymphatic leukemia (17). Within recent years, the demonstration that antiglobulin serum would agglutinate red cells in certain cases of erythroblastosis (18, 19) and acquired hemolytic anemia (20) has focused considerable attention on "sensitization" of red cells as one of the factors responsible for their accelerated breakdown. Since a positive Coombs test may often be demonstrated in cases of acquired hemolytic anemia that have stopped hemolyzing following splenectomy (20), the presence of antibody globulin on the red cell is not the sole factor accounting for rapid red cell destruction. It may be, in addition, a matter of the concentration of antibody attached to the red cell since Evans and Duance (21) showed that the activity of hemolysis is associated with maximum amount of absorbed antibody. One must also consider the quantity of antibody-globulin produced by an abnormal spleen (22). This factor may be operative in patients with acquired hemolytic anemia but not in normals. That some splenic mechanism contributes to hemolysis may be argued from the frequent arrest of hemolysis following splenectomy (16, 23). Wagley et al. (22) showed that the spleen may be an important source of antibody globulin, and Evans and Duance (21) reported that splenectomy may result in a sharp decrease in the amount of antibody attached to the cell.

Two of our cases of chronic lymphatic leukemia were noted to be persistently anemic despite frequent blood transfusions. In case 2 (A. A.) there was a sustained rise in hemoglobin following TEM therapy, so that transfusions were not necessary during a five month period in a patient who had been receiving at least 2-4 packed cell units a month for two years. Unfortunately, the possible effect of TEM on hemolysis was not studied here. In case 1 (A. C.) a hemolytic syndrome was more clearly evident, as manifested by (1) absence of a rise and an actual drop in hemoglobin following a transfusion; (2) a direct positive Coombs test and (3) a very short red cell survival time. Group O blood was transfused into this patient and differential agglutination counts were performed by the Ashby technique* (24). The curve of red cell survival indicates rapid destruction, within a period of two weeks, of transfused O cells as well as the patient's own A cells (fig. 5). As noted previously, TEM failed to influence the persistent hemolysis in this patient. Since a positive Coombs test persisted after TEM and gave us no indication of the tempo of hemolysis, we had to rely on red cell survival studies, repeated 2-3 weeks after TEM had been given. There was still a rapid hemolysis of transfused as well as the patient's own cells (fig. 6). Without actually quantitating the amount of antibody on the red cell (21) we do not know if TEM had any effect on the amount of antibody globulin produced.

2. TEM and Hepatic Injury. It will be noted from fig. 2 that after 15 mg. of TEM, case 1 (A. C.) showed an acute exacerbation of hepatic insufficiency.

* Miss Lorraine Moore did most of the differential agglutination counts.

This was manifested by a rapidly deepening icterus, itching, a rise of serum bilirubin to 10 mg. % and a sharp rise in urine urobilinogen with the appearance of bile in the urine.

Liver injury with nitrogen mustard has been quite uncommon in the absence of pre-existing hepatic damage, and several liver function studies have shown no change (25). Nevertheless, icterus as well as focal necrosis of the liver have been described following nitrogen mustard therapy (26, 27).

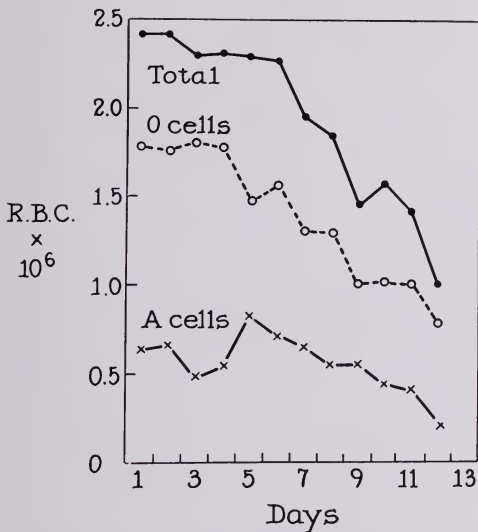


FIG. 5. Curve of red cell survival of donor (Group 0) cells transfused into patient A. C. (Case 1). The counts were made by the differential agglutination technique (Ashby 24). These studies were made coincident with the initial administration of 15 mg. TEM.

Caution should therefore be observed in the use of TEM in jaundiced patients, in whom icterus and hepatomegaly represent considerable liver cell damage.

B. Polycythemia Vera: In one case of polycythemia vera, good marrow-suppressing effects were achieved and maintained on TEM therapy. It is of considerable interest that with dosages of TEM which would ordinarily cause severe leucopenia, the white count was well maintained but marked depression occurred in the erythroid series. This may be further proof of the major effect of mustards on actively proliferating tissue (28). Schullenberger and Watson (29) studied the effects of nitrogen mustard on the marrow of patients with polycythemia vera and concluded that this drug probably has a greater effect on erythropoiesis than on myelopoiesis. We found that at the time of the greatest

depression of hemoglobin this patient's marrow showed a fairly normal normoblastic proliferation. When erythropoiesis "escaped" from the TEM and the hemoglobin rose, the marrow revealed a tremendous spurt in erythroblastic-normoblastic proliferation.

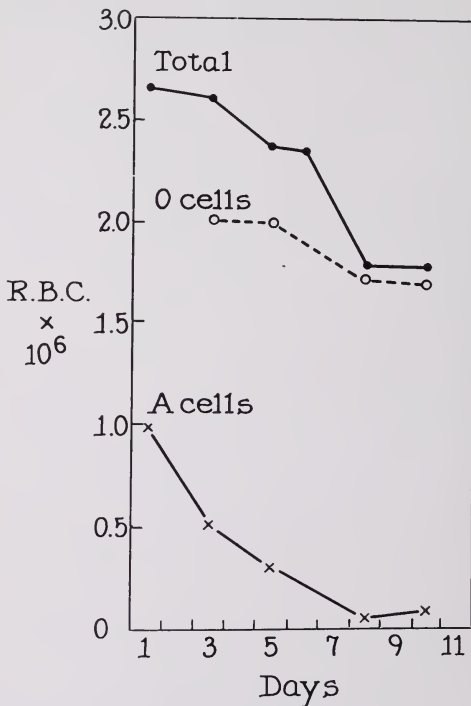


FIG. 6. Curve of red cell survival repeated in patient A. C. (Case 1) three weeks after the administration of 15 mg. TEM.

Schullenberger and Watson (29) further recognized these pancytotoxic effects of the usual nitrogen mustard course to control polycythemia, and suggested the use of small, repeated courses "at shorter intervals than has been the custom, with the aim of finding a dosage schedule which may result in adequate depression of mitoses of the erythropoietic cell". With oral TEM one can achieve this effect. In our single case spaced therapy was necessary, but adequate control

of the disease was maintained. It is possible that other cases of polycythemia vera may exhibit a sustained remission after a single adequate dose of TEM.

SUMMARY

1. A new oral mustard-like drug, triethylene melamine (TEM) has been used in the treatment of chronic lymphatic leukemia and polycythemia vera.

2. The initial "course" of therapy we employed was 5 mg. for two to three days. Unpleasant side effects were practically absent. As with intravenous nitrogen mustard therapy, TEM will induce hematopoietic depression. Further TEM therapy should await evidence of active bone marrow regeneration. Caution should be used in the administration of TEM to patients with hepatomegaly and jaundice.

3. TEM is a potent lymphoid-shrinking agent, although its effects in this respect may be only temporary. In far advanced "radio-resistant" cases of chronic lymphatic leukemia, lymphadenopathy, hepatosplenomegaly, and intra-abdominal masses receded. Obstructive symptoms due to local lymph node compression were similarly relieved. Hemoglobin and platelets may rise, the total white count fall, but lymphocytic infiltration in the marrow persists. In one case, acquired hemolytic anemia secondary to chronic lymphatic leukemia was not affected by TEM.

4. In a case of polycythemia, TEM induced a sustained marrow depression with restoration of peripheral blood count and blood volume to normal. Initial phlebotomy was not done. Unpleasant side effects after repeated doses of TEM were not observed.

5. In cases of chronic lymphatic leukemia and polycythemia, maintenance therapy, in the form of 2.5 to 5.0 mg. of TEM monthly or every two months, was kept up. Our aim was to maintain a therapy-induced remission. After protracted use of TEM, there was some evidence to indicate an increased sensitivity of the marrow to further therapy, or a "cumulative toxicity", and care must be taken to avoid abrupt, large doses.

REFERENCES

1. GILMAN, A.: Therapeutic Applications of Chemical Warfare Agents. *Fed. Proc.*, 5: 285, 1946.
2. ——— AND PHILIPS, F. S.: Biological Actions of Nitrogen Mustards. *Science*, 103: 409, 1946.
3. KARNOFSKY, D. A.: Nitrogen Mustard in the Treatment of Neoplastic Disease. *Adv. Int. Med.*, 4: 1, 1950.
4. HADDOW, A., KON, G. A. R., AND ROSS, W. C. J.: Effects Upon Tumors of Various Haloalkylarylamines. *Nature*, 162: 824, 1948.
5. BURCHENAL, J. H., CROSSLEY, M. L., STOCK, C. C., AND RHOADS, C. P.: The Action of Certain Ethylenimine (Aziridine) Derivatives on Mouse Leukemia. *Arch. Biochem.*, 26: 321, 1950.
6. LEWIS, M. R. AND CROSSLEY, M. L.: Retardation of Tumor Growth in Mice by Oral Administration of Ethylenimine Derivatives. *Arch. Biochem.*, 26: 319, 1950.
7. PHILIPS, F. S. AND THIERSCH, J. B.: Nitrogen Mustard-like Action of 2, 4, 6, Tris-(Ethylenimino)-S-Triazine, and Other Bis (Ethylenimines). *J. Pharmacol. & Exper. Therap.*, 100: 398, 1950.

8. RHOADS, C. P., KARNOFSKY, D. A., BURCHENAL, J. H., AND CRAVER, L. F.: Triethylene Melamine in the Treatment of Hodgkin's Disease and Allied Neoplasms. *Tr. A. Am. Physicians*, 50: 136, 1950.
9. KARNOFSKY, D. A., BURCHENAL, J. H., ARMSTEAD, G. C. JR., SOUTHAM, C. M., BERNSTEIN, J. L., CRAVER, L. F., AND RHOADS, C. P.: Triethylene Melamine in the Treatment of Neoplastic Disease. *A. M. A. Arch. Int. Med.*, 37: 477, 1951.
10. RHOADS, C. P.: Nitrogen mustard in the Treatment of Neoplastic Disease. *J. A. M. A.* 131: 656, 1946.
11. SPURR, C. L., JACOBSON, L. O., SMITH, T. R., AND BARRON, E. S. G.: The Clinical Application of Methyl-Bis-B Chloroethyl Amine Hydrochloride to the Treatment of Lymphomas, and Allied Dyscrasias. *Approaches to Tumor Chemotherapy*. Ed. F. R. Moulton. *Am. Assoc. Adv. Science.*, 1947.
12. JACOBSON, L. C., SPURR, C. L., BARRON, E. S. G., SMITH, T., LUSHBAUGH, C., AND DICK, G.: Nitrogen Mustard Therapy. *J. A. M. A.*, 132: 263, 1946.
13. SHULLENBERGER, C. C., WATKINS, C. H., AND KIERLAND, R.: Experiences with Nitrogen Mustard Therapy. *J. A. M. A.*, 139: 773, 1949.
14. BAUER, R. D. AND ERF, L. A.: Clinical Effects of Nitrogen Mustard on Neoplastic Diseases. *Am. J. Med. Sc.*, 219: 16, 1950.
KARNOFSKY, D. A. AND BURCHENAL, J. H.: Present Status of Clinical Cancer Therapy. *Am. J. Med.*, 8: 767, 1950.
15. DAMESHEK, W. AND SCHWARTZ, S. O.: Acute Hemolytic Anemia. (Acquired Hemolytic Icterus, Acute Type.) *Medicine*, 19: 231, 1940.
16. SINGER, K. AND DAMESHEK, W.: Symptomatic Hemolytic Anemia. *Ann. Int. Med.* 15: 544, 1941.
17. STATS, D., ROSENTHAL, N., AND WASSERMAN, L. R.: Hemolytic Anemia Associated with Malignant Disease. *Am. J. Clin. Path.*, 17: 585, 1947.
18. COOMBS, R. R. A., MOURANT, A. E., AND RACE, R. R.: Weak and "Incomplete" Rh Agglutinins. *Lancet*, 2: 15, 1945.
19. COOMBS, R. R. A., MOURANT, A. E., AND RACE, R. R.: A New Test for the Detection of Weak and "Incomplete" Rh Agglutinins. *Brit. J. Exper. Path.*, 24: 225, 1945.
20. BOORMAN, K. E., DODD, B. E., AND LOUIT, J. F.: Hemolytic Icterus (Acholic Jaundice) Congenital and Acquired. *Lancet*, 1: 812, 1946.
21. EVANS, R. S. AND DUANE, R. T.: Acquired Hemolytic Anemia. I. The Relation of Erythrocyte Antibody Production to Activity of the Disease. II. The Significance of Thrombocytopenia and Leucopenia. *Blood*, 4: 1196, 1949.
22. WAGLEY, P. F., CHEN, S. C., GARDNER, F. H., AND CASTLE, W. B.: Studies on the Destruction of Red Blood Cells. VI. The Spleen as a Source of a Substance Causing Agglutination of the Red Blood Cells of Certain Patients with Acquired Hemolytic Jaundice by an Anti-Human Serum Rabbit Serum (Coombs Serum). *J. Lab. & Clin. Med.*, 33: 1197, 1948.
23. SINGER, K. AND MOTULSKY, A. G.: The Developing (Coombs) Test in Spherocytic Hemolytic Anemias. *J. Lab. & Clin. Med.*, 34: 768, 1949.
24. ASHBY, W.: The Determination of the Life of the Transfused Blood Corpuscles in Man. *J. Exper. Med.*, 29: 267, 1919.
25. GOODMAN, L. S., WINTROBE, M. M., DAMESHEK, W., GOODMAN, M. J., GILMAN, A., AND McLENNAN, M. T.: Nitrogen Mustard Therapy. *J. A. M. A.*, 132: 126, 1946.
26. ZANES, R. P., DOAN, C. A., AND HOSER, H. A.: Studies in Hodgkin's Syndrome. VII. Nitrogen Mustard Therapy. *J. Lab. & Clin. Med.*, 33: 1002, 1948.
27. DAMESHEK, W., WEISFUSE, L., AND STEIN, T.: Nitrogen Mustard Therapy in Hodgkin's Disease, Analysis of 50 Consecutive Cases. *Blood*, 4: 338, 1949.
28. FRIEDENWALD, J. S.: The Action of Nitrogen Mustards and Related Substances on Cell Division. *Ann. New York Acad. Sc.*, 51: 1432, 1951.
29. SHULLENBERGER, C. C. AND WATSON, C. H.: Effects of Nitrogen Mustards on the Bone Marrow in Polycythemia Vera. *Ann. Int. Med.*, 33: 841, 1950.

EMOTIONAL FACTORS IN THE ETIOLOGY AND THERAPY OF HYPERTHYROIDISM*

THEODORE LIDZ, M.D.†

New Haven, Conn.

There are many personal reasons for my being pleased and honored to talk in this hospital, but there is special reason to feel privileged to discuss the particular topic assigned in *this* lecture series, for in 1930 Dr. Eli Moschcowitz published a paper, "The Nature of Graves' Disease" (1), which focussed attention upon the frequency with which emotional trauma preceded the onset of the illness. The concept was not new, for the precipitation of thyrotoxicosis by a shock had been noted since the first descriptions of the syndrome over a hundred years before; and numerous investigators had emphasized the importance of emotional disturbances in hyperthyroid patients. Dr. Moschcowitz' observations were more far-reaching, and were accompanied by bolder and more courageous statements. He found that emotional traumata preceded the onset of the illness in at least 80 per cent of his cases, and he called attention to the unstable personality integration of these patients. This contribution was followed by another in conjunction with Dr. A. Lorand (2), which was one of the early psychosomatic studies to utilize modern dynamic concepts; and if his paper did not actually stimulate, it certainly encouraged two rather remarkable studies of the emotional factors in the etiology of hyperthyroidism by Agnes Conrad (3) and by Bela Mittelman (4).

These three papers of the early thirties presented case histories that contain obvious similarities; and between them not only clearly indicated the very high incidence of cases in which illness had its onset shortly after an emotionally traumatic occurrence, but also show an unusual agreement concerning the traits and basic attitudes of the personalities of the patients studied. These careful studies of an illness of unknown etiology were surely among the most definitive leads for future investigations, but they appear to have exerted meagre influence upon the course of research or upon the treatment of thyrotoxicosis. Although the recent studies by Whitehorn and myself (5) (6) (7) and by Ham, Alexander, and Carmichael (8) have evoked more resonance, and although they may contain advances in crystallizing the understanding of the personality structure of hyperthyroid patients, the significant data, that is, the evidence for the importance of emotional trauma and the relationship of traumatic occurrence to the personality integration of the patient was presented almost twenty years ago. The neglect of these studies may have been due to the arousal of new fields of investigation by the discovery of the thyrotropic hormone, but more probably,

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† From the Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut.

simply because the material advanced did not coincide with the dominant medical concepts of the period. Therefore, it seems well to indicate in passing that it is not counter to current physiologic knowledge or concepts to consider emotional trauma as an etiologic factor in hyperthyroidism. Despite the many advances in the study of the endocrine balance related to hyperthyroidism and the even greater advances in therapy in recent years, the etiology of the disease remains unknown, and the knowledge of the functions of the thyroid gland continues to be rather vague. The interrelationships between the thyroid and the adrenal glands become increasingly challenging. It is accepted that the adrenal medulla plays a major part in the preparation of the body to meet danger, which is an emotional stress. The picture of thyroid overactivity in turn is to a very large degree the picture of sensitization to adrenergic activity. Further, some experiments suggest that the secretion of epinephrin stimulates secretion of thyrotropic hormone. An hypothesis may be suggested that the thyroid contributes to the defense against prolonged danger or stress by augmenting the short-lived epinephrin effects by keeping the body sensitized to small amounts of epinephrin secretion, and by mobilizing energy through promoting general tissue catabolism beyond that produced by the rapid mobilization of blood sugar by epinephrin. Such conjectures are outside the field of clinical study. However, I may be permitted to state that the clinical evidence would indicate that study of the physiology of the thyroid gland has concentrated too much upon the homeostasis of heat regulation and too little on the defenses against stress. After all, thyrotoxicosis in a patient is a picture of terror. The tremor, the sweating, the rapid heart rate, the labile blood pressure, the mobilization of sugar, the bulging eyes, well led to the designation of thyrotoxicosis as "crystallized fright".

However, the evidence for the importance of emotional factors in hyperthyroidism is not based on physiologic experimentation, but upon clinical study. Most important has been the consistency with which all psychiatrically oriented observers have found that the illness begins at a time of severe emotional turmoil. Second, observers are struck by remarkable similarities between the types of circumstances which apparently precipitate the illness in the patients in their own series as well as in the series of other investigators. Third, and perhaps most interesting, is the constant reappearance of similar features in the developmental history, the basic attitudes, and the defensive maneuvers by which these patients strive to maintain their emotional equilibrium. In a preliminary study (4) of fifteen hyperthyroid patients, I sought to recall attention to these facets of the problem of hyperthyroidism, and noted the similarities of my own findings and conclusions to those of earlier investigators. Now, while in the process of reviewing the psychiatric studies of eighty hyperthyroid patients, carried out with varying degrees of intensity, I shall try to present some of the more pertinent impressions obtained; emphasizing certain defects in the personality development and structure which seem common to hyperthyroid patients and which leave them prone to be overwhelmed emotionally when specific critical defensive patterns are demolished. Finally, I shall make some comments upon how the

understanding of the deficiencies in the personality integration can be helpful in the medical and psychiatric management of hyperthyroid patients.

As has been noted, the various recent studies of series of hyperthyroid patients agree that at least 80 per cent of the patients had suffered from severe emotional disturbances at the time of the onset of their illness. This is a high and significant figure in view of the difficulties in gaining the necessary cooperation to investigate the emotional lives of large numbers of patients. It has been suggested by both Dr. Moschcowitz and by Dr. Mittelmann that only psychoanalytic study of the exceptions can determine whether or not emotional trauma is a necessary precursor to thyrotoxicosis. In each of the several series of patients which we have studied for differing reasons there were one or two patients who at first appeared to be exceptions because no story of any particularly upsetting circumstance could be elicited. However, it is just these cases which now seem among the most convincing corroborations of the hypothesis that emotional disturbance is a prime factor in the onset of thyrotoxicosis because they served to prove the rule, in the true meaning of the expression, through turning out to be among the most typical cases studied. Insofar as possible, I shall attempt to use these cases in presenting illustrative material.

For practical purposes I shall group the emotional upsets which confront the patients at the time they become ill into three general categories. First, there are acute and shattering traumata which overwhelm a person whose life seems to have been reasonably well organized. Examples of such occurrences are frequent in the older literature, such as a farmer who developed Graves' disease a few days after his wife and newborn child were burned to death while he made desperate but unavailing efforts to rescue them (9). Such cases are seen, but constitute a small minority. Thus a colored man became ill shortly after he had accidentally killed a white man with his automobile in a southern city. He was terrified and plagued by constant recurrent nightmares of a lynching he had witnessed as a small child.

In the second group the emotional disturbance is brought about by an occurrence which does not always sound gravely traumatic, and the person who becomes ill seems to have been reasonably well adjusted, but an occurrence had shattering consequences because it struck the vulnerable point in the patient's defenses, and left him prey to what was feared most. Let me cite an example.

A thirty year old single colored woman was transferred to the medical service following an hysterectomy, when her rapid pulse rate was found to be due to thyrotoxicosis. She was quite depressed when she learned that her uterus had unexpectedly been removed, and cried abysmally because she would never be able to have children. She felt that her whole life depended on having children, and she said outright, "Who will take care of me when I am old the way I take care of my father? Even if I marry, my husband will be an old man when I am old." She was a devoted youngest child. Her mother had died when she was two, and the father had been both a mother and a father to her. He was a strict, overly religious man with a strong sense of right and wrong, who had devoted himself to raising his six children after his wife's death. The patient felt that she

would never marry while the aged father lived, for it was her pleasure and privilege to take care of him now that her older siblings had all married. Although she had been going with a boy friend for over seven years, she would never marry him because she felt that a person couldn't trust marriage. She had been trying to have a baby outside of wedlock because she wanted to have a baby to take care of now, and who would take care of her when she became old. It would have seemed that the hysterectomy to this woman might have been a blow to her equilibrium sufficient to have been considered as an etiologic factor in the hyperthyroidism. However, it was found that she had been hyperthyroid for four to five months prior to the operation, although it had been overlooked. It was difficult to keep the patient in the hospital because she felt, as do many hyperthyroid women, that some terrible disaster would befall her father or her siblings if she were not at home to protect them by her obsessive concern for them. As a matter of fact, her brother's house did burn down while she was in the hospital.

The patient was followed in the thyroid clinic, and it was considered that her personality makeup and her basic orientation toward life were characteristic of hyperthyroid women. There was evidence of early sibling rivalry with concern that the siblings were more favored by the father, but she had won out by remaining the good child who took care of father after all the others had departed. She had identified with him very strongly in his high ethical standards and his method of gaining affection by devotedly doing for others. The patient constantly felt insecure unless she was able to be useful to other people, as if she felt she could not be loved if she were not bestowing. There was little faith in any relationship except those knit by the bond of the family, particularly that of the parent-child relationship. She had been unable to move out of the home, and the problem of finding a husband was very secondary to the attachment to her own family. These attitudes are considered quite typical of hyperthyroid patients, but it appeared as if the pattern were working effectively. It was assumed on the basis of experience that something had occurred that had made the adjustment untenable, and that the patient felt lost, deserted, and did not know how to readjust. She was placed on n-propyl thiouracil and seen every other week. For many months there was no indication that her hyperthyroidism had been started by any particular event. We discussed the family situation, her reluctance to marry, and returned to the problem of whom she would have after her very aged father died. Her initial attitude remained, that there was no sense in relying upon marriage. Then one day she started to talk of one of the older brothers. She had always thought that he was the only person on earth who might be as good as her father. Her eyes glowed as she spoke of him. He had been the last to marry. She had always expected that the two of them would remain together, keeping up the family home after the father died. Then she began to cry. He had married about four months before her operation. For a long time she had thought she would be unable to attend his wedding because she had sobbed uncontrollably whenever she had thought of it. It had been a terrible time for her. When some one called her attention to the fact that she and the bride were as like as "two peas in a pod" she felt better and was able to pull

herself together. She continued in this vein until I commented that she was quite a jealous person. She said that she wasn't jealous of the bride, but she couldn't stand having the brother leave her. When I replied that of course her brother couldn't marry *her*, she blushed violently, then laughed, and said that a sister can do a great many things for a brother, but she can't marry him. She then went on to tell that she was certain that it was at the time of the brother's marriage that she had become ill. Subsequent events indicated the import of this exchange, for not long thereafter she came in and announced very shyly that things had been looking different, and she had decided to marry her boy friend. It was a good marriage for this patient, because she was able to settle down next door to the father and attend to his needs before and after work each day, and because her husband fostered rather than resisted the attachment to her family.

Among many other things, the case illustrates the difficulty in finding and citing the traumatic event. A brother's marriage is not usually considered an untoward occurrence. Yet, the patient's entire orientation toward life and her security rested upon maintaining the relationship with her father, with the assurance that after he died she would continue to live with her brother. She had felt quite certain that neither would desert her because she had made herself so essential to both of them. With this security she was able to reject marriage as being too uncertain because it was not based upon familial interrelationship. If you will pardon a mixed metaphor, I will conjecture that with her father at bat and her brother on deck, all she needed was a baby in the hole as a replacement for the remote future. Everything was changed by the brother's marriage, and, further, she was confronted by the failure of her basic security operations.

The third group of patients is comprised of individuals who are more clearly and obviously disturbed than the patient who has just been presented, whose life had continued on a reasonably even keel until her way of achieving security by becoming indispensable to others failed. These patients suffer from severe obsessive and phobic anxieties, or are pushing themselves to extreme degrees of compulsive activity in their attempts to ward off the danger of being isolated and rejected. Their defenses are failing and are shored up by secondary defenses which in turn provoke new difficulties and create even greater anxiety. Unable to accept the actual circumstances, they close their eyes to them, and in unrealistic fashion continue in their old patterns rather than attempt to solve their difficulties. I wish to accentuate what happens in this group of patients because they present the most difficult therapeutic problems, and because when patients are studied carefully more and more seem to fall into this group in which severe obsessive anxiety has the upper hand at the time the hyperthyroidism ensues.

The case used as an illustration is chosen because the patient had been the one patient in the first series of fifteen reported whose hyperthyroidism had not been related to a period of emotional turmoil at the time the paper was written. This woman had undergone two subtotal thyroidectomies and an orbital decompression for malignant exophthalmus. Later the patient returned and sought psychiatric help because she did not know how to cope with her husband's daily

or twice daily request to have sexual relations, which she was unable to refuse lest he be killed immediately after and she would regret her denial for the remainder of her life. She felt herself torn in two by the competitive demands of her son and husband for her affections. She passed most of her evenings in dread terror when her husband was away at work, fearing that all sorts of disasters might befall him, and unable to let her son sleep alone in his room lest he die while she was away from him. In the daytime she could not let her son play out of her sight and was filled with torment when she forced herself to allow him to go to school unaccompanied. She was unable to feel any resentment over the demands placed upon her by her son and husband, and reassured herself that she could not be feeling hostile for she was constantly worrying that something might happen to them. The pattern had gone back into her early life when the slightest feelings of anger toward her mother or her older sister would be replaced by the fear that they might get killed. She soon became aware of her lifelong hostility toward her sister who had dominated the family scene. She had never fought nor competed, but had sought to gain mother's affection by becoming very much like mother and by being nice to people. While the sister went out to work and filled the role of a son in the family, the patient stayed home, and after marrying settled down in a house across the street from her parents. The covert struggle continued between the patient and her sister for the mother's affection, and later for the affection of the patient's son. The patient developed Graves' disease at a time when she had to move from the vicinity of the parental home because of her husband's occupation, and then, because she was ill with renal colic, the son went to stay with the mother and sister and began to show more affection toward the sister than to her. Her instability increased as animosity rose toward her husband and son because of the demands they made upon her, and toward the sister for presuming the mother; when unable to accept any feelings of antagonism or resentment, she compulsively tried to satisfy the needs of all of these people, while the obsessive concern for their safety kept her on the verge of a constant state of panic. Even as she discussed these difficulties, the patient could continue to maintain that she was extremely happy, and when her attention was called to her unbearable fears she was able to deny that meant she was unhappy because she said, "Happiness is a state of mind. I believe I'm happy and so I am."

The inability to face the conflicting demands placed upon them, and the ability to close one's eyes to the actual situation, in some patients goes beyond all reasonable bounds and inevitably leads to disaster; while the anxieties provoked by the obsessive concerns for the husband or children are sources of chronic subacute panic.

A thirty-five year old woman became hyperthyroid during her fifth pregnancy and had to be hospitalized because of intractable vomiting. There had been two previous hypertensive toxemias and the patient had been warned that another pregnancy would seriously endanger her life. She had promised to utilize the contraceptive information given, but had neglected it completely. She had claimed that she had not recognized any symptoms of pregnancy during the

first three months when a therapeutic abortion might have been performed. At the same time she told naively of various attempts to abort herself during the first two months of pregnancy by repeatedly falling down the stairs, and of how she could not understand how it was possible for her not to have vomited up the baby at the rate she had been going. These irrationalities and many others in her life revolved about her Catholicism. She was an oldest child who at the age of eleven had taken over the care of her younger siblings when her mother became ill, and had become close to mother and like mother. She had married a divorced Protestant man, but insisted that neither her husband's religion nor his divorce bothered her at all, although she concealed his previous marriage and his Protestantism from her children, and in totally unrealistic manner tried to pretend to her children that their half sister by the husband's previous marriage was not related to them. Almost at the same time that she expressed her unconcern at being cut off from the church, she would talk of her terror of dying without benefit of communion. There were innumerable difficulties with the children because of the severe restrictions she placed upon them because she was too anxious to let them play out of her sight or hearing. At one time she was insisting on signing out of the hospital, and explained that it was because the children were going to a picnic where they would go swimming. She was terrified of water and had to be there to safeguard them. During the preceding summer she had almost drowned when one of the children had stayed submerged a little longer than expected, and she had jumped to the rescue with all of her clothes on. She continued to divulge numerous similar fears. After purchasing a new oil burner, she would rush to the cellar each time the burner switched on to make sure that it would not catch fire or explode. She became worn through lack of sleep, but solved the problem by sleeping in the basement for several nights until convinced that the oil burner was no danger. Her fears had forced her father to rewire the entire house; and the family to move into the country where the children would be safer from traffic. Still the boys had to cross a highway to go to school; and she insisted that they go separately so that only one would be killed if an accident occurred.

Some of the traits repeatedly found by psychiatrists who have studied hyperthyroid patients were noted in the histories which have been cited. Various observers have commented upon features in the fundamental attitudes that are contradictory: the unusual attachment to the mother figure that persists into adult life, and the early premature striving for independence; the need for dependency, and the tendency to take care of other people; the attempts to identify with mother and the fear of maternal responsibility; the frequency with which they express fears of childbirth and the statistically validated fact that they have more children than the average woman (8). It has also been noted that 50 per cent are the oldest children in the family; that deaths in the immediate family frequently occurred during the patient's early childhood; that the sexual adjustment of the woman is inordinately poor, and that the husband plays a secondary role in their lives; and that they tend to seek to attach at least one child to them by strangling oversolicitude.

I have simply cited some of these characteristics, and now wish to tie them together into a composite picture, which, though inaccurate for any given patient, would seem to have a high degree of pertinence for almost all; and to suggest a specific theme based upon a type of defensive maneuver which can be recognized through its many variations as the motivating force in their developmental history.

The fear of desertion or of rejection by a parental figure was an early threat of such magnitude that it could never be allowed to recur. The histories of these patients are spotted by the early death of a parent, the withdrawal of the mother from the family circle, but most commonly, the threat came in the form of the real or imagined preference of the mother for another sibling. The patient becomes hostile to the mother for having deserted in favor of the other sibling, and toward the sibling for having seduced the mother; but the fear of being isolated from mother gains the upper hand. The patient solves the problem by endeavoring to become essential to the mother—to prove that in the long run she is the good child and that mother will come to appreciate her. She demands little and relieves mother of her burden by taking mother's responsibilities upon herself prematurely. The other children may have their innings now, but the patient's turn will come after the other children have left home. In the terms of Agnes Conrad (3), the patients make desperate lifelong struggles to win mother's approval and to achieve likeness to her at the same time that they fear her pain. The pattern of gaining affection by compulsive doing for others is established. When a patient can no longer do for others and be useful to them, she feels it is impossible to be loved. The early hostilities are buried under excessive solicitude, but they have laid the foundation for the compulsive, phobic pattern. The importance of maternal affection is magnified through the belief that mother love is the only important and significant relationship upon which a person can rely, as if the jealousy of the care given a sibling made it the only desirable goal. But mother will die some day and they tend to protect themselves by having children. They believe that if they bestow the same all-embracing solicitude on their children as they had wished to gain from mother, the child will never leave them. One hears such remarks from them as: "Mother was good. She gave me *things*, but I give *myself* to the children." "The trouble with this country is that mothers stop caring for their children after they are grown." Often the husband is chosen because he will not interfere with the relationship to the parental home, or because he is a passive individual who can be treated and controlled as a child. Thus, the patients develop with a fundamental fear of isolation from the needed person, and a terror of desertion, and have gained a means of protecting themselves by making themselves essential to others through constant bestowing. Hostility is denied and repressed because it threatens the relationship. With this type of security operation they feel that they can ward off the ultimate disaster and control the persons who are important to them. It is difficult to know whether such security operations can lead to a personality structure that is satisfactorily integrated. A study of hyperthyroid patients is limited to instances in which these maneuvers fail. It would seem,

though, that they contain weaknesses that make catastrophe almost inevitable. Mother cannot live forever; a child who has been made resentful by the strangling oversolicitude will often rebel; the husband, chosen because he is dependent, is apt to continue his attachment to his own mother, or when neglected by the patient in favor of the children will turn against her. At such times the patient is left helpless, betrayed and enraged, and it is then that the hyperthyroidism is apt to ensue. Often, however, the patient is not yet defeated, but makes more frantic and desperate efforts to achieve her goals by compulsive doing for others, and begins to create further traumatic situations by being unable to accept the inevitable. The goodness is not reciprocated, and she grows increasingly hostile. The hostility is undone by the obsessive fears that harm may come to the children, the mother, or the spouse. The patient must be constantly protecting them by the magic of her worrying. The obsessive undoing controls the hostility which cannot be tolerated, but it is an uneconomic defense for it gives rise to constant panicky anxiety that mounts proportionately as the feelings of rejection and hostility increase. The patient then begins to live in a rather constant state of terror, and it is at such times that I believe hyperthyroidism is apt to start in some patients. The constant, severe, terrifying anxiety may somehow be related to the need to mobilize thyroid activity to cope with the constant stress.

It is then, when the patient is confronted by the isolation and rejection that she has been warding off since early childhood, that the hyperthyroidism is apt to ensue. In some instances it is when the means of attaching persons to her by compulsive doing fails, either through accident or through infidelity or desertion. In other patients, when the loss is not tangible, but emotional, the defeat is denied and fought against; while the hostility aroused by the betrayal is managed by a secondary defense of obsessive and phobic denial of the hostilities, which is dynamically related to the primary compulsive maneuver. The patients, in such cases, become hyperthyroid when these secondary defenses decompensate because of the continuing danger. It has already been noted that such obsessive undoing of hostility is uneconomic, for it engenders more and more anxiety.

It is obvious that not all persons who develop such defensive patterns become hyperthyroid even when their defenses fail and precipitate severe emotional disorders; nor does the development of a psychosis prevent the psychosomatic disturbance from occurring, for psychoses are not uncommon among hyperthyroid patients. It can only be said at present that the evidence indicates that hyperthyroidism is one of the several alternative outcomes of the developmental difficulties which have been described. It seems probable that the endocrine disorder results when some additional factor is a determinant. One might conjecture a variety of possible factors, such as the concomitant endocrine imbalance of pregnancy, puberty, or menopause; or something still more specific to the thyroid pituitary relationship, such as a congenital deficiency or a previous non-toxic dysfunction as commonly occurs in women during puberty or pregnancy.

The hypothesis that emotional factors are of import in the etiology of Graves' disease does not require such specific dynamics of personality structure; but rests primarily upon the consistency with which emotional disturbances antecede

the illness. I have not dwelt upon documenting the relationship between emotional stress and the onset of hyperthyroidism because it would seem to me that this had been done adequately in numerous articles. I think that it should be possible to say, as did Raymond Crawford (10) in the 1890's "that sudden emotion or prolonged worry commonly sets in motion the symptoms will be so universally conceded as not to demand extensive illustration." I have rather concerned myself with an attempt to increase the insights into the personality structure of these patients, because, if reasonably correct, they can be extremely helpful in the treatment of the illness.

The use of the various antithyroid drugs, and more recently of radioactive iodine, has changed the treatment of hyperthyroidism considerably; recognition that the hyperthyroid patient is in a critical life situation has also implemented treatment. Relief from the toxic state of hyperthyroidism is insufficient because the patient needs help in re-orienting; in establishing new defenses, or in forming new attachments and in making progress toward a more mature relationship with people; or at times help in re-establishing or preserving the old relationships through a change in the patient's attitudes toward them. In general, the therapist seeks to promote growth through helping the patient overcome the distorting and frustrating adherence to an outmoded pattern; often to make it possible for the marital relationship to supplant the tie to the parental family, or to help the patient relinquish her strangling hold upon her children and attain a more satisfactory relationship with them.

In working with a relatively large number of patients it is helpful if the psychotherapist can count on his theoretical assumptions to help select what is meaningful in what the patient tells. If the analogies between the problems presented by different patients are sufficiently accurate to permit carry over from case to case, we have arrived at an increase in the degree of predictability which we seek in all scientific investigation.

Some such assumptions have proved helpful. The younger group of single patients are confronted with the loss of the significant parental figure, usually the mother; at times through death or departure; but at times because their own instinctual drives or growth have forced them away from what they believe is acceptable to mother. The young married woman is often struggling with the pull between the parental and the marital home. She is apt to be constantly concerned about her mother when separated from her. She had hoped to find a new source of security with the husband or through having children, but, as noted, has usually found a relatively passive partner. If the husband seems neglectful even to the extent of being concerned about his own family, she projects her own attachments, becomes hostile, frightened by her hostility, and wishes to return home. In this dilemma, the childhood pattern is repeated, and she cannot make demands upon her parents rather than relieve them of responsibilities. Poor sexual adjustment increases the conflict. If in these circumstances she becomes pregnant, she feels trapped, cut off forever from the security of her home. When the hyperthyroidism has started in relationship to pregnancy early in marriage, it has always been found that the patient had been on the

verge of leaving her husband. Later in marriage the illness is apt to be precipitated by the infidelity or gross neglect of the husband. In later years the source of conflict comes when the child or foster child who has been selected as the particular object of her solicitude, and whom she expects to remain faithful, leaves home or threatens to leave. At times the marital situation becomes so difficult that the patient can no longer continue to maintain the home and the children she needs to have with her.

Cognizance of these general trends often permits one to cut through the abundance of material to focus on the pertinent. A 22 year old woman becomes moderately hyperthyroid early during her first pregnancy. Marriage and the general life situation sound as if they are more than satisfactory. However, when the physician inquires how she felt about leaving her home to live with her in-laws, the patient suddenly bursts into tears. Because her husband was in the army she had remained with the aunt who had raised her since the age of five, until the husband returned from overseas, when she moved to his home. She became intensely unhappy, worrying about her aunt, and resentful of the mother-in-law's criticism of her and the favoring of her husband. She spent hours crying when alone, and felt so desperate that she was about to return to the aunt when she found herself pregnant. After discussions of her concerns and fears, the impulse to flee to her aunt dissipated rapidly, and her attachment to her husband became fortified when he started to seek a home of their own and to take a stand against his mother's attempts to dominate the patient. With the help of n-propyl thiouracil the hyperthyroidism soon subsided and the delivery and postpartum period were uneventful. When last seen, the patient had moved into a happy and successful marital relationship.

A somewhat older woman was torn between 2 unsatisfactory attachments; one to her alcoholic husband whom she had married in desperation, and one to her more or less psychotic mother. However, the critical period started when the mother insisted upon permitting a younger epileptic brother who was violently dangerous to return home. Focussing upon the patient's endeavors to gain her mother's affection and approval, although mother was no longer a protecting figure but a serious liability, permitted the patient to emancipate herself sufficiently to reorganize her life pattern.

A woman in her fifties became hyperthyroid and no precipitant could be found. Her life story revealed that all of her efforts had gone into re-establishing a home for her unwanted daughter after divorcing her alcoholic husband soon after the marriage. It was considered that the daughter must have threatened to leave home, but the patient denied such inquiries. However, the daughter told that her mother had become ill immediately after she had told her mother of her plans to marry. Then the attention of the psychotherapy could be directed toward the reasons why the "desertion" of this unwanted child was so dangerous to the patient.

The psychiatric treatment, then, is not directed toward "curing" the thyroid disease; but toward helping patients develop new attitudes that will release them from the fears which in adult life are often highly unrealistic. At times,

particularly in older patients, the therapy takes the opposite turn, and seeks to make it possible for the patient to fall back upon a dependent role which she had felt forced to renounce. For example, a middle-aged woman felt impelled to leave her husband when she discovered his infidelity, unable to tolerate such betrayal. However, after a number of discussions, the patient decided that the home and the husband's kindness to her were more important, and she could manage to overlook his brief period of infidelity.

The understanding of the importance of the emotional plight of the hyperthyroid patient has had consequences that are more pervasive than those involved directly in psychotherapy. At the Johns Hopkins Hospital the thyroid clinic was reorganized as a combined venture, with the social worker and psychiatrist playing a major role (6). The medical management of the hyperthyroid patient requires carrying the patient through the initial period during which the turbulence is increased by the thyrotoxic state. The social worker interviewed all new patients and let them know that she was available to discuss difficulties that arose in following the medical regimen or in the general life situation. The relationship with the social worker formed a fixed relationship for the patient when the medical personnel shifted over the year or two that these patients were carried on n-propyl thiouracil. Physicians became alert to what the person talked about, and ceased attributing all of the difficulties to the thyrotoxic state. The doctor-patient relationship became more meaningful for both parties. The fidelity to the therapeutic regimen, essential to successful medical therapy, improved remarkably because of the personal nature of the relationship established.

With hospitalized patients it was found that the insistence upon leaving the hospital prematurely was not due to the general restlessness of hyperthyroid patients alone, but often because of the obsessive fears that their children would be harmed if unprotected by them. The hospital regulations were altered to permit their young children to visit, with beneficial results. Recently Dr. Ferris of Cincinnati General Hospital informed me that recognition of the hyperthyroid woman's compulsive needs to be helpful to others led to a change in routine, permitting these patients to be out of bed and helping minister to other patients, with marked diminution in restlessness and agitation.

Before closing, I would like to venture some impressions that evolved from the studies of the personalities of these patients, which have had some influence upon the choice of the various therapies now available. When it appeared that the continuity of a reasonably well organized life had been disrupted by an acute and devastating episode, such as in the case of the colored man who had accidentally killed a white man, it was considered that with minimal psychiatric help the patient would recover after a relatively short period of treatment with n-propyl thiouracil. Actually, in this instance, it was correctly predicted that the medication could be withdrawn after about two months of treatment. At the other extreme were the patients already described, who are caught up in frenzied, compulsive activity, and are constantly terrified by their obsessive fears of harm coming to others. As has been indicated, the defenses of these patients have already crumbled and they are seeking to manage on the basis of

secondary uneconomic anxiety-provoking defenses. They carry sources of recurrent upsets in themselves. They are apt to do poorly on medical management, failing to adhere to the regimen, or relapsing soon after withdrawal of the medication even after long periods of treatment. Indeed, they do not do particularly well after surgical treatment either, for the cases of recurrent hyperthyroidism or of malignant exophthalmus appear to derive from within this group. If the thyroid remains quiescent they almost always continue to suffer from severe emotional disturbances. However, it would seem advisable to simplify the complicated situation by surgical ablation and then concentrate on the emotional problems involved. Most cases fall between these extremes, and the understanding of the emotional difficulties taken in conjunction with the medical condition of the patient has helped determine the strategy of medical as well as of psychiatric management. A rather complex example in which decision involved numerous factors was presented by a seventeen year old boy who was extremely toxic and almost hypomanic in his behavior. He had been living with a severely rejecting and alcoholic father and a paranoid grandmother who was a fanatical religious cultist. His three brothers had all developed marked anti-social trends. The mother had left home after the father had brought his mistress and her four children to live with the family. The mother was incapable of supporting the children and had never really tried, although from time to time she had sought to rescue one of the older boys. The patient had finally run away from his father, despite the father's threats that he would kill the patient, and sought to live out the fantasy of finding a good and protecting mother. His fantasy was shattered when he found his mother a dependent, semi-invalided woman, living in a dependent and probably homosexual relationship with an older woman, who was by now fed up with the mother's uncontrollable offspring. The mother would not or could not accept the boy in the home. Because of the extreme toxicity, his hypomanic behavior and the complexity of the situation, it was decided to perform a subtotal thyroidectomy as soon as feasible, which was then followed by careful foster home placement on a farm where he found a satisfactory father figure for the first time in his life, and was legally protected from the father's threats, but which at the same time provided occasional contacts with the mother that permitted him to hold to a somewhat idealized picture of her.

I have sought to present some illustrations of divergent approaches, omitting, of course, some flagrant failures. The failures, as is often the case, have often taught most, and have continued to challenge our concepts of the personality integration of these patients as a group.

SUMMARY

The presentation this evening has tried to convey something of the reasons for the conviction that emotional factors are extremely important in the etiology of hyperthyroidism, and how an understanding of these factors serves to modify treatment. I have included some of my recent speculations concerning a type of personality defense that seems common to most hyperthyroid patients. I would

like to add, for my psychiatric colleagues who are present, that the study has been rewarding beyond the applications to hyperthyroidism, for it has led to concentrating upon the psychopathology of the deficiencies of a certain pattern of uncompensated obsessive compulsive defense.

Attention is also drawn to the study of the pattern of security operations by which the child had sought to master a major insecurity of early childhood, and which persisted, and in turn helped pattern the life, the fear never mastered, but defended against; and the consideration of a specific threat to these basic defenses as the precipitant of the illness. The concept differs from studies of specificity of "personality patterns" or of types of stress as etiologic factors in psychosomatic disorders, although clearly related to such concepts.

In closing, I would like to quote from Dr. Moschcowitz's paper of 1930 (1), when, in discussing the cure of hyperthyroidism by thyroidectomy he said: "The basal metabolism decreases rapidly, the patient gains weight, the pulse drops, the tremor subsides. The last symptom to disappear is the exophthalmus. It often persists throughout life. However, that which never disappears is the personality of the patient. The patient is still sensitive, emotional, restless, temperamental, sanguine, etc. In this sense the patient with Graves' disease is never completely cured, though he may be socially and economically restored." Although I cannot report cure of many patients in this fuller meaning of the term "cure", I hope that the way has been indicated which might lead to treatment of hyperthyroid patients that is really adequate.

REFERENCES

1. MOSCHCOWITZ, E.: The Nature of Graves' Disease. *Arch. Int. Med.*, 46: 610, 1930.
2. LORAND, A. AND MOSCHCOWITZ, E.: A Psychoanalytic Interpretation of the Constitution in Graves' Syndrome. *J. Nerv. Ment. Dis.*, 79: 136, 1934.
3. CONRAD, A.: The Psychiatric Study of Hyperthyroid Patients. *J. Nerv. Ment. Dis.*, 79: 505, 1934.
4. MITTELMANN, B.: Psychogenic Factors and Psychotherapy in Hyperthyreosis and Rapid Heart Imbalance. *J. Nerv. Ment. Dis.*, 77: 465, 1933.
5. LIDZ, T.: Emotional Factors in the Etiology of Hyperthyroidism. *Psychosom. Med.*, 11: 2, 1949.
6. ——— AND WHITEHORN, J.: Psychiatric Problems in a Thyroid Clinic. *J. A. M. A.*, 139: 698, 1949.
7. ——— ———: Life Situations, Emotions and Graves' Disease. *Psychosom. Med.*, 12: 184, 1950.
8. HAM, G. C., ALEXANDER, F., AND CARMICHAEL, H. T.: A Psychosomatic Theory of Thyrotoxicosis. *Psychosom. Med.*, 13: 18, 1951.
9. GOODAL, J. S. AND ROGERS, L.: The Effects of the Emotions in the Production of Thyrotoxicosis. *M. J. and Rec.*, 138: 411, 1944.
10. CRAWFORD, R.: Graves' Disease: An Emotional Disorder. *King's Coll. Hosp. Rep.*, 3: 45, 1897.

THE INEFFECTIVENESS OF KHELLIN IN THE TREATMENT OF ANGINA PECTORIS*

GEORGE C. LEINER, M.D. AND SIMON DACK, M.D.

Since the application of khellin and its derivatives to the treatment of angina pectoris due to coronary insufficiency (1, 2), there have been conflicting reports concerning its efficacy when administered orally or parenterally. The early clinical studies by Anrep and associates (3) indicated that a favorable response was obtained in the majority of patients treated with this drug. Subsequent clinical studies (4-9) appeared to corroborate their findings, since symptomatic improvement was noted in the great majority of patients treated with oral doses of khellin ranging between 120 and 450 mgm. daily. Lian and Charlier (10) observed improvement in 150 of 200 patients following the intramuscular administration of injectable khellin, and similar good effect of injectable Ammivin was recently reported by Kleiber (11). The above results were based on the effect on subjective symptoms such as frequency and severity of anginal attacks and ability to walk longer distances without pain.

The effect of the drug on objective tests appeared to confirm the findings based on subjective improvement. Thus, Dewar and Grimson (12) reported that oral administration of khellin prevented anginal pain following an exercise test in 7 of 12 patients tested, although it had no effect on the electrocardiographic changes after exercise. Similarly, Best and Coe (13) felt that khellin favorably altered the response to exercise and anoxemia in several of 9 patients tested.

The above findings of subjective improvement and improved response to exercise have not been confirmed by other observers. Greiner and coworkers (14) compared the effect of khellin administered orally and a placebo tablet on the frequency and severity of anginal pain in 39 patients. They found no significant difference. Since the doses ranged from 50 to 150 mg. daily, the findings of these authors have been criticized on the ground that the daily dose was too small in some of the patients. Scott and coworkers (15) observed no significant effect from oral doses on subjective symptoms or response to exercise in the majority of their 21 patients whom they followed for a period of six months. However, in a more recent paper, Scott and Seiwert (16) reported an improved exercise electrocardiogram in 3 of 14 patients studied with a crystalline khellin. The observations of Russek and his group (17) also indicated that the administration of khellin in daily doses of 240 mgm. orally or 200 mgm. intramuscularly had no significant effect on the electrocardiographic response to exercise in five carefully tested patients. Finally, Hultgren, Robertson and Stevens (18) failed to observe a beneficial effect on the exercise tolerance test following the oral and parenteral administration of the drug in eight patients. Although the oral administration of the drug seemed to decrease the number of anginal attacks induced by effort in an appreciable percentage of their cases, these investigators could not deter-

* From the Department of Medicine, The Mount Sinai Hospital, New York, N. Y.

mine whether this was due to an actual beneficial effect on the coronary circulation or to decreased physical activity caused by toxic reactions to the drug.

In this report we wish to present the results obtained with several khellin preparations in a group of patients treated in the Cardiac Clinic. Our findings appear to indicate that khellin in moderate or large oral doses has no significant favorable effect on the frequency or severity of anginal pain in patients with chronic coronary insufficiency.

MATERIAL AND METHOD

Twenty-two patients in the Cardiac Clinic were selected for study. Of these, seven did not return for adequate follow-up interviews and examinations after treatment was started. We may assume that these patients did not improve while taking the drug, for they probably would have returned for replenishment of their medicine if they had felt better. The results are based on the findings in the remaining 15 patients, 12 of whom were men and 3 were women.

All the patients had moderate or severe angina of effort of many months' or several years' duration and had been observed frequently in the clinic during this period. The diagnosis of chronic coronary insufficiency due to coronary sclerosis was confirmed by careful cardiac examinations including frequent electrocardiograms and a 2-step exercise test when indicated. Past treatment had included the usual drugs such as sedatives, nitroglycerine and other available coronary vasodilators without significant beneficial effect. The preparations of khellin studied were the following: 1.0 kello^{*} tablets, containing 50 mg. of khellol glucoside; 2. Ammivin[†] tablets containing 20 mg. of pure khellin; 3. Khelltron[‡] tablets, containing 20 mg. of crystalline khellin.

Treatment was initiated by administering a placebo tablet indistinguishable in appearance from the respective khellin tablets. All other medication was discontinued except for nitroglycerine during an anginal attack. The patients were advised not to change their usual daily routine of activities. They kept a daily record of the number of anginal attacks, the daily consumption of nitroglycerine and the exercise tolerance as gauged by the amount of walking required to induce anginal pain. They were interviewed and examined once weekly. This method of evaluating drugs for angina pectoris is similar to that employed in this clinic for many years (19).

After the patients had taken the placebo tablet three times daily for one or two weeks and the effect on their symptoms was noted, the khellin preparation was administered. They were never made aware of the change from the placebo tablet to the drug. The khellin preparation was administered in doses of 1 tablet three times daily, and after one week it was increased to 2 tablets three times daily. In some of the patients receiving Okello^{*}, the dose was finally increased to 3 tablets three times daily (450 mgm daily). The highest dosage was maintained for two to three weeks.

RESULTS

The results of our observations are summarized in Table 1. Only four of the fifteen patients reported that they felt better while receiving khellin, as manifested by less frequent anginal attacks and decreased requirement of nitroglycerine during the test period. One patient improved while taking Ammivin (3 to 6 tablets daily) and one while taking Khelltron (3 tablets daily). The latter patient refused to continue taking the drug for more than one week because it produced gastric discomfort. Two patients reported relief while

* Supplied by Otis Laboratories Inc.

† Supplied by The National Drug Co.

‡ Supplied by Casimir Funk Laboratories, Inc.

taking Okello (300 to 450 mgm. daily); one of these continued to feel better even after the drug was discontinued.

Six patients stated that they felt worse while taking khellin. One patient claimed that the placebo tablet was more effective than Ammivin and another stated that it was just as effective.

Unpleasant side-effects referable to the gastro-intestinal tract were noted by only 4 patients. These included anorexia (Ammivin), nausea (Khelltron), vomiting (Okello) and gastric discomfort (Khelltron). No effect on the heart rate or blood pressure was noted in any patient on repeated examination.

TABLE 1

CASE	PLACEBO	OKELLOL			AMMIVIN		KHELLTRON	
	1 or 2 t.i.d.	1 t.i.d.	2 t.i.d.	3 t.i.d.	1 t.i.d.	2 t.i.d.	1 t.i.d.	2 t.i.d.
1.	U	U						
2.	U	U	U					
3.	U	U	U	U				
4.	U	U	U	U				
5.	I				I	I		
6.	U		I	I				
7.	U		U					
8.	I					U		
9.	U		U					
10.	U		U	U				
11.	U		U	U				
12.	U		I	I	I			
13.	U						U	
14.	U						U	U
15.	U						I	

U..unimproved.

I..improved.

COMMENT

Our clinical observations indicate that there was no significant improvement in the severity or frequency of angina pectoris following the administration of moderately large doses of khellin. Only a small minority of treated patients reported significant relief of symptoms as compared to a placebo tablet. These observations suggest that khellin is of little value in the routine treatment of angina pectoris due to coronary artery disease.

Although the evaluation of the therapeutic effect of khellin in this study was based on the subjective response of the patient, an attempt was made to exclude the factors of suggestion and psychogenic effect in our patients. This was achieved by the control administration of identical placebo tablets and the avoidance of over-enthusiasm on the part of the physicians.

The lack of therapeutic effect in our patients is in marked contrast to the previously reported (2, 3, 10) pharmacological effect of the drug. These experimental observations have indicated that khellin has a selective cardiac action characterized by coronary vasodilation and improved cardiac contraction. The

early clinical studies seemed to confirm these experimental observations but subsequent reports as well as our studies have failed to duplicate these results uniformly.

Although frequent gastro-intestinal symptoms were observed by previous observers following the administration of other khellin preparations, such side-effects were infrequent in our patients. This indicates that khellol glucoside (Okello), which was the drug used in 10 of the 15 patients, is non-toxic even in doses of 450 mg. daily in divided doses. This was true also of Ammivin and Khelltron, administered to the other 5 patients, which contain crystalline khellin.

SUMMARY

Fifteen patients with long standing angina pectoris were treated with several oral khellin preparations. Increasing doses of these drugs were clinically ineffective in the majority of patients. Improvement, judged by the decreased number and severity of anginal attacks, was observed in only four patients. Six patients felt worse while taking the drug. Gastro-intestinal side effects occurred in four patients.

The unsatisfactory clinical effects of oral khellin are in contrast with the pharmacological effects observed in animal experiments.

REFERENCES

1. KENAWY, M. R. AND BARSOUM, G. S.: Ammi Visnagi in the Treatment of the Anginal Syndrome. *Gaz. Faculty Med. Cairo*, 13: 33, 1945.
2. ANREP, G. V., BARSOUM, G. S., KENAWY, M. R., AND MISRAHY, G.: Ammi Visnagi in the Treatment of the Anginal Syndrome. *Brit. Heart J.*, 8: 171, 1946.
3. ———, KENAWY, M. R., AND BARSOUM, G. S.: The Coronary Vasodilator Action of Khellin, *Am. Heart J.*, 37: 531, 1949.
4. ROSENMAN, R. H., FISHMAN, A. P., KAPLAN, S. R., LEVIN, H. G., AND KATZ, L. N.: Observations on the Clinical Use of Visammin (Khellin). *J. A. M. A.*, 143: 160, 1950.
5. ARMBRUST, C. A., JR., AND LEVINE, S. A.: Treatment of Angina Pectoris with Preparation of Khellin (Ammi Visnagi). *Am. J. M. Sc.*, 220: 127, 1950.
6. OSHER, H. L., KATZ, K. H., AND WAGNER, D. J.: Khellin in the Treatment of Angina Pectoris. *New England J. Med.*, 144: 315, 1951.
7. DREZNER, H. L. AND HOROSCHAK, S.: Angina of Effort: Its Treatment with Crystalline Khellin. *J. Med. Soc. New Jersey*, 48: 116, 1951.
8. NIEL, K.: Khellin bei Angina Pectoris. *Wien. klin. Wchnschr.*, 63: 729, 1951.
9. CONN, J. J., KISSANE, R. W., KOONS, R. A., AND CLARK, T. E.: The Treatment of Angina Pectoris with Khellin. Part 1. *Ann. Int. Med.*, 36: 1173, 1952.
10. LIAN, C. AND CHARLIER, R.: Etude experimentale et clinique de la Khelline. *Acta Cardiol.*, 5: 373, 1950.
11. KLEIBER, E. E.: Parenteral Administration of Ammivin (Khellin) in the Treatment of Coronary Disease. *Ann. Int. Med.*, 36: 1179, 1952.
12. DEWAR, H. A., AND GRIMSON, T. A.: Khellin in the Treatment of Angina of Effort. *Brit. Heart J.*, 12: 54, 1950.
13. BEST, M. M. AND COE, W.: Effect of Khellin on Coronary Artery Insufficiency as Evaluated by Electrocardiographic Tests. *Circulation*, 2: 344, 1950.
14. GREINER, T., GOLD, H., ET AL.: Method for Evaluation of Effects of Drugs on Cardiac Pain in Patients with Angina of Effort. Study of Khellin (Visammin). *Am. J. Med.*, 9: 143, 1950.

15. SCOTT, R. C., IGLAUER, A., GREEN, R. S., KAUFMAN, J. W.,¹ BERMAN, B., AND MCGUIRE, J.: Studies on the Effect of Oral and Parenteral Administration of Visamin (Khellin) in Patients with Angina Pectoris. *Circulation*, 3: 80, 1951.
16. ——— AND SEIWERT, V. J.: The Treatment of Angina Pectoris with Pure Crystalline Khellin. *Ann. Int. Med.*, 36: 1190, 1952.
17. RUSSEK, H. I., REGAN, F. D., ANDERSON, W. H. DOERMER, A. A., AND NAEGELE, C. F.: Effect of Khellin in Coronary Artery Insufficiency as Evaluated by Electrocardiographic Tests. *New York State J. Med.*, 52: 437, 1952.
18. HULTGREN, H. N., ROBERTSON, H. S., AND STEVENS, L. E.: Clinical and Experimental Study of the Use of Khellin in Treatment of Angina Pectoris. *J. A. M. A.*, 148: 465, 1952.
19. MASTER, A. M., JAFFE, H. L., AND DACK, S.: The Drug Treatment of Angina Pectoris. *Am. J. M. Sc.*, 197: 774, 1939.

THE EFFECT OF INTRANEURAL INJECTION OF BACITRACIN IN RABBITS*

PAUL TENG, M.D. AND SIDNEY W. GROSS, M.D.

New York, N. Y.

Peripheral neuritis as a complication of the intramuscular injection of penicillin has been observed occasionally (1, 2, 3). It has been demonstrated in experimental animals that the neuritis is attributable to the introduction of the material directly into the parenchyma of the nerve, especially when an oily base is used (3). The injection of streptomycin into a peripheral nerve produces similar degenerative changes. The purpose of this experiment was to determine the effect of bacitracin solution when injected into peripheral nerves.

METHOD AND MATERIAL

Nine rabbits of 4.5 to 6.6 lbs. of body weight were used. The animals were anesthetized with intravenous sodium nembutal, 60 mg. for 5 lbs. of body weight. The posterior and lateral aspect of the upper part of both hind legs were shaved and the skin was sterilized with tincture of iodine. With the animal in the prone position, the sciatic nerve was isolated through a longitudinal incision about 4.0 cm. long. The left sciatic nerve was used as a control into which 0.2 c.c. of physiological saline solution was injected. Into the right sciatic nerve 2,000 units of bacitracin in 0.2 c.c. of physiological saline solution were instilled through a tuberculin syringe and a 24 gauge needle. The pH of the bacitracin solution was 6.72. The site of injection was marked with a black silk stitch to the epineurial sheath. The wound was closed with silk.

Postoperatively, the animals were examined daily for 7 days and then at semi-weekly intervals until the time of sacrifice. The motor power was tested (1) by means of the spread reflex, elicited by suddenly lowering the upheld animal. The amount of spreading of the toes indicates the degree of damage to the nerve; for the interruption of the sciatic nerve abolishes the reflex. (2) One hind leg was held in each hand of the examiner and the force of kicking and withdrawal was tested. (3) The movements of the hind legs were carefully observed when the animal was hopping outside the cage. Pain sensation was tested by pin-pricking the foot.

The animals were killed in groups with intraperitoneal sodium nembutal. Three rabbits were killed 1 week after the injection (#1, 2, 3), three at the end of 3 weeks (#4, 5, 6), and 3 at 6 weeks (#7, 8, 9). The wound of each hind leg was reopened and examined. A segment of the sciatic nerve including the site was removed for microscopic examination.

Results

When 0.2 c.c. of normal saline solution was injected into the left sciatic nerve, the control side, the fluid was seen rapidly and evenly distributed along the trunk of the nerve and there was no obvious change in shape of the nerve sheath or the size of the nerve. The injection of the same amount of bacitracin solution, however, invariably produced a fusiform bulge at the site of instillation, in every instance. This was probably due to the higher viscosity of the bacitracin solution than that of the physiological saline solution.

No weakness was observed in the injected legs of the 9 rabbits during the period of observation before the animals were killed at the scheduled time. In only 2 rabbits (#3, 9), which were killed 3 weeks and 6 weeks, respectively, after the injection of bacitracin into the right sciatic nerve, was the spread reflex found slightly diminished. This appeared on

* From the Neurosurgical Service of the Mount Sinai Hospital, New York

the second day of operation and persisted until the animals were sacrificed. Nevertheless, paralysis or sensory defect was not found.

Three rabbits (#1, 2, 3) were killed 1 week after the intra-epineurial injection. The healed wound was reopened and the sciatic nerve as well as the surrounding tissues were examined. The left sciatic control nerve looked normal. The surrounding soft tissues showed signs of mild inflammatory changes. On the side of bacitracin injection, the inflammatory changes were more marked than the controls. In one rabbit the soft tissues were edematous and there was an accumulation of serous exudate in the wound (#1). The nerve sheath appeared slightly congested.

Three rabbits (#4, 5, 6) were killed 3 weeks after the injection. Minimal amounts of scar tissue were found in the wound, both of the controls and of the bacitracin injected sides. In only one sciatic nerve into which bacitracin had been instilled was there slight thickening of the epineurial sheath (#6).

TABLE I

Degree of degeneration of the sciatic nerve of the rabbit after the intra-epineurial injection of physiological saline or bacitracin solution

NO. OF RABBIT	DURATION OF SURVIVAL	LEFT SCIATIC NERVE INJECTED WITH 0.2 C.C. NORMAL SALINE (CONTROL)	RIGHT SCIATIC NERVE INJECTED WITH 2,000 UNITS OF BACITRACIN IN 0.2 C.C. NORMAL SALINE
	<i>weeks</i>		
1	1	Minimal	Minimal
2	1	Minimal	Minimal
3	1	Minimal	Marked*
4	3	Normal	Minimal
5	3	Normal	Minimal
6	3	Normal	Moderate
7	6	Minimal	Normal
8	6	Minimal	Moderate
9	6	Normal	Marked*

* Animal showed diminished spread reflex of the right hind foot.

Three rabbits (#7, 8, 9) were sacrificed 6 weeks after the intra-epineurial injection. The findings in this group of animals were similar to those of the second group. Only one sciatic nerve which had been injected with bacitracin solution showed a slight degree of thickening of the epineurial sheath (#9).

A segment of each sciatic nerve was removed from the 9 rabbits, including the site of injection which was marked with a black silk suture. The specimens were fixed in 20% formalin.

Microscopic Observations

The specimens were embedded in paraffin, sectioned at 5 to 6 μ and stained by the hematoxylin-eosin, Marchi's and Bielschowsky methods.

In the specimens of the 3 rabbits (#1, 2, 3) killed one week after the injection, the control sciatic nerve showed monocyctic and lymphocytic and occasional polymorphonuclear cell infiltration of the soft tissues surrounding the nerve trunk. Similar cellular infiltration was seen in the epineurial sheath as well as the nerve parenchyma. The nerve bundles displayed a mild degree of fragmentation and vacuole formation (fig. 1a). The vacuoles were irregular in size, 10 to 30 microns in diameter and some contained eosinophilic material. The same degree of changes were found in the nerve on the bacitracin injected side of 2 rabbits. The right sciatic nerve of the third animal (#3, fig. 1b) showed a marked degree of fragmentation and vacuolization of the nerve bundles with marked monocyctic and lympho-

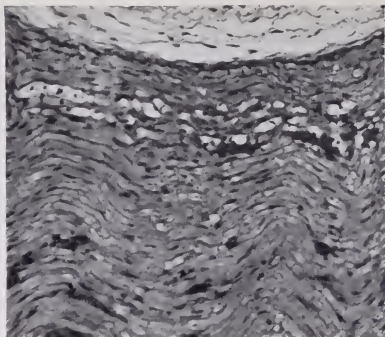
*a**b*

FIG. 1. *a*. Left sciatic nerve, rabbit #3, showing minimal degenerative changes, 1 week after the intra-epineurial injection of 0.2 c.c. of physiological saline (control). Hematoxylin-eosin stain. $\times 175$

b. Right sciatic nerve of the same rabbit, showing marked degenerative changes, 1 week after the injection of 2,000 units of bacitracin in 0.2 c.c. of physiological saline solution. $\times 175$

cytic cell infiltration of the epineurial sheath as well as the nerve parenchyma. The surrounding soft tissues were edematous. It was in this rabbit that the spread reflex was found diminished.

The left control sciatic nerve of the second group of rabbits (#4, 5, 6) looked normal in every instance under the microscope. The right sciatic nerve showed a minimal amount of vacuoles scattered among the nerve bundles in two of the three animals. This change was found in a moderate degree in the third animal with proliferation of the Schwann's, and endoneurial cells and of the fibrocytes.

Of the three rabbits killed 6 weeks after the intra-epineurial injection, the control nerve showed minimal degenerative changes in 2 and normal in the other. On the side of bacitracin injection, the finding was normal in one and a moderate and a marked degree (fig. 2) of degeneration in the remaining two respectively.

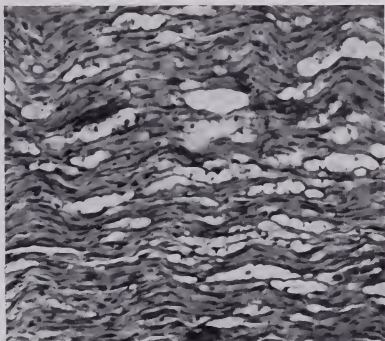


FIG. 2. Right sciatic nerve, rabbit #9, showing marked degeneration 6 weeks after the intra-epineurial injection of 2,000 units of bacitracin in 0.2 c.c. of physiological saline solution. Hematoxylin-eosin stain. $\times 175$

DISCUSSION

The intra-epineurial injection of penicillin, streptomycin (3) or bacitracin into a peripheral nerve may cause neuritis. As shown in the above experiment, even the injection of normal saline solution into the sciatic nerve of a rabbit may cause microscopic degenerative changes. Five of the 9 controls displayed a minimal degree of fragmentation and vacuolization of the nerve bundles of the sciatic nerve into which 0.2 c.c. of physiological saline solution had been instilled.

Although up to date there has been no clinical report of peripheral neuritis caused by the intramuscular injection of bacitracin, such an involvement may occur should this antibiotic by error be instilled into a large nerve trunk. This experiment demonstrates that the intraepineurial injection of 2,000 units of bacitracin in 0.2 c.c. of normal saline solution causes more degenerative changes in the sciatic nerve of rabbits than the controls into which the same amount of normal saline solution had been injected. However, there was no obvious weakness or paralysis which could be elicited by repeated neurological examination. The only positive findings were the microscopic changes in the sciatic nerves and the diminished spread reflex on the side of bacitracin instillation. The loss of spread reflex is a known indication of impaired nerve function. In two of the 9 rabbits (#3, 9) the spread reflex was found diminished. This clinical finding corresponded to the marked microscopic changes of the related sciatic nerve

which had been injected with bacitracin solution. In the rest of the animals, the changes were minimal in 4, moderate in 2 and normal in one. None of the animals showed any abnormal clinical signs. The result of this experiment is compatible with the observation of Tarlov and associates (3) on the intraneurial injection of penicillin or streptomycin. Their findings showed that the neuritic changes were more marked when an oily base preparation of penicillin had been injected into the sciatic nerve of rabbits.

Nowadays with the indiscriminate use of antibiotics, it is hard to evaluate either the benefit of any particular antibiotic, or to find out which one is responsible for any complication which may occur as a result of therapy. Antibiotics are often used in a shotgun fashion. One of us (P.T.) recently saw a patient who developed a left foot drop 2 weeks after the intramuscular injections of penicillin, bacitracin and streptomycin. It was difficult to tell in this case which one of the 3 antibiotics was the cause of the paralysis, for all three were simultaneously administered.

SUMMARY

1. Eight of nine sciatic nerves of rabbits into which 2,000 units of bacitracin in 0.2 c.c. of physiological saline solution were injected, showed degenerative change: 2 marked, 2 moderate and 4 minimal. In the controls, 5 out of 9 sciatic nerves showed minimal degeneration by microscopic examination.

2. The spread reflex, a sign of impaired nerve function, was found diminished on the side of bacitracin in 2 instances.

3. In the administration of bacitracin or any other antibiotic, the injection should be kept remote from the course of any large nerve trunk.

REFERENCES

1. BROADBENT, T., ODOM, G. AND WOODHALL, B.: Peripheral Nerve Injuries from Administration of Penicillin. *J. A. M. A.*, 140: 1008, 1949.
2. KOLB, L. C., AND GRAY, S. J.: Peripheral Neuritis as a Complication of Penicillin Therapy. *J. A. M. A.*, 132: 323, 1946.
3. TARLOV, I. M., PERLMUTTER, I. AND BERMAN, A. J.: Paralysis Caused by Penicillin Injection; Mechanism of Complication—A Warning. *J. Neuropathology & Exper. Neurol.*, 10: 158, 1951.

PSEUDOCYST OF THE PANCREAS*

ALEXANDER RICHMAN, M.D.

The appearance of a left upper quadrant mass in the course of an acute abdominal disease is strongly suggestive of acute pancreatitis with pseudocyst formation. In most cases, the diagnosis can be corroborated by exploratory operation, but occasionally a situation is encountered in which the clinical course does not warrant surgery and the nature of the mass can be only speculated upon. In such cases, the history, the laboratory findings and the radiographic studies are the only means of elucidating the problem. A case illustrating some difficulties encountered is reported.

CASE REPORT

History: E. W., Adm. #630456, a man, aged 43 years was admitted to The Mount Sinai Hospital on September 1, 1951, complaining of severe upper abdominal pain of two days' duration, which had a sudden onset and aroused him from a sound sleep; it persisted, uninfluenced by self-administered remedies. The pain was a dull ache radiating to both lower quadrants of the abdomen. Low grade fever and chilly sensations were present.

In the two week period prior to the onset of his pain, weakness, anorexia and vague abdominal distress had contributed to a feeling of ill health. Five days before admission, a blackish, tarry stool had been passed. In the past 7 years he had been troubled by distress following meals. He admitted that he was a heavy drinker with a daily intake of 20 cans of beer. On the day of the onset of his illness he had imbibed an unusually large amount of beer.

Examination. The patient was extremely obese, acutely ill, appeared anxious and was dyspneic. There was no cyanosis. Temperature was 102°F, pulse, 100, respirations, 32. The heart sounds were rapid and regular; the blood pressure was 130/80. The lungs were clear. The abdomen was distended. Considerable tenderness was elicited in both upper quadrants. No masses were felt. There was no rebound tenderness. Rectal examination revealed no tenderness or fullness. There was no edema.

Laboratory Findings included a white blood count of 20,800 with 80 per cent polymorphonuclear leucocytes and 20 per cent lymphocytes, blood amylase of 30 Somogyi units (normal 80-120) and blood calcium of 8.7 mg/100 cc. Urine showed a trace of albumin and no sugar. Flat films of the abdomen revealed no evidence of intestinal obstruction or of dilatation of small bowel. X-ray studies of the chest (fig. 1) showed no abnormality in the position of the diaphragm or any evidence of lung disease.

Course. An abdominal puncture was performed in the right lower quadrant and 3 cc. of reddish brown cloudy fluid was obtained which showed numerous white blood cells and red blood cells. The fluid was cultured and reported as showing B. Coli. No pancreatic ferments were demonstrated.

A provisional diagnosis of acute pancreatitis was entertained and the appropriate therapy was instituted, including parenteral fluids, antibiotics, gastric suction and banthine in 50 mg. doses every 4 hours. The subsequent course was stormy with temperature persisting at a level of 102°F. for several days. Tachycardia and tachypnea were constant. On the third day icterus was noted, the quantitative bilirubin being reported as 1.2 mg. per 100 cc. On the following day, a large, soft mass was felt in the left upper quadrant which moved slightly with respiration. The upper border of this mass paralleled the left costal margin, and its lower limit could not be defined. Dullness and diminished breath sounds were present at the base of the left lung from the ninth interspace down.

* From the Department of Surgery, The Mount Sinai Hospital, New York. Presented at the Gastrointestinal Conference, The Mount Sinai Hospital, Jan. 8, 1952.

Fluoroscopy revealed elevation and fixation of the left diaphragm. X-ray studies of the chest (fig. 2) verified the presence of the high fixed diaphragm. The lung fields were clear. Abdominal X-ray films revealed a large soft tissue density in the left upper abdomen,

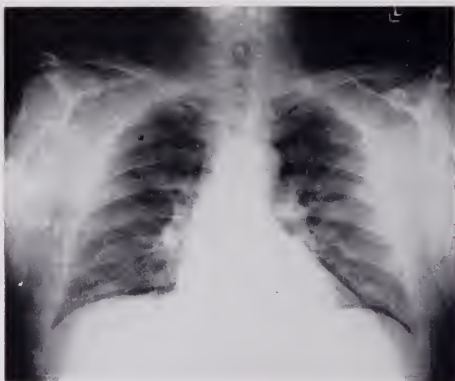


FIG. 1. Roentgenogram of the chest, showing the usual relationship of the left and right leaves of the diaphragm.

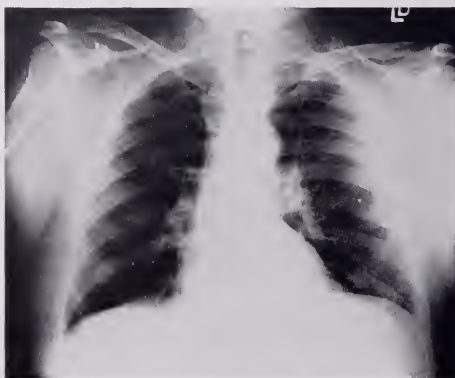


FIG. 2. Roentgenogram of the chest after the appearance of the pancreatic pseudocyst indicating elevation of the left leaf of the diaphragm.

with an ill defined margin. Barium enema was carried out and showed the splenic flexure to be displaced downward by this mass (fig. 3). Intravenous pyelogram revealed that the mass was displacing the left kidney caudad. Barium meal examination (fig. 4) revealed evidence of extrinsic pressure on the lesser curvature of the stomach. The stomach and



FIG. 3. Barium enema, showing downward displacement of the distal transverse colon and splenic flexure.



FIG. 4. Roentgenogram showing displacement of lesser curvature of the stomach by a soft tissue mass.

duodenal bulb showed no ulcer or other intrinsic disease. The duodenal curve was not abnormal.

Repetition of blood amylase studies revealed values of 40 mg. on the fourth day, 115 mg. on the fifth day, 30 mg. on the eighth day and 60 mg. on the tenth day; at no time was any elevation demonstrated. Bilateral edema was noted on the 12th day and in view of the absence of cardiac failure or of disturbed renal or hepatic function, was thought to be due to pelvic thrombophlebitis which is sometimes seen with acute pancreatitis. This cleared before his discharge from the hospital in the course of treatment.

On the fourteenth day there was a drop in temperature and subjective improvement was manifest, but the mass persisted and was described as being the size and shape of a small football; its lower margin, however, still could not be delineated. On the 18th day, a pancreatic function test (secretin) was carried out and the following values were recorded: Amylase, 10.6 u/kg; bicarbonate 110 meq/l and vol. 2.4 cc/kg., all within normal limits. The biliary pigment response was normal.

For the next 8 days, his general condition improved. Temperature was 98.6° F., his appetite and feeling of well-being returned. The mass became somewhat smaller and in view of this benign course, it was deemed advisable to send the patient for convalescent care, later to be observed in the follow-up clinic. On several follow-up visits he had no complaints and the mass continued to decrease in size.

On his last follow-up visit, 4 months after discharge, no mass was felt and he stated that he felt perfectly well despite the resumption of his alcoholic routine.

DISCUSSION

In this case it may be stated that a pseudocyst was observed to develop during the course of acute pancreatitis, as proved by the absence of a mass on admission and its subsequent appearance during the patient's stay in the hospital, as shown by physical examination and radiographic studies. The alcoholic history is not uncommonly encountered in acute pancreatitis and is thought to be directly causative in the pathogenesis (1, 2). The absence of confirmatory laboratory evidence in the form of elevated blood enzyme values was disconcerting in the first days of the illness, but was explainable upon discovery of the mass. Howard *et al.* (3) have shown that the mechanism of the increased amylase in acute pancreatitis is the retrograde passage of the enzyme from the obstructed ducts through the acinar cells into the capillaries and into the blood stream. If sufficient destruction of pancreatic tissue occurs, these enzymes will filter into the necrotic collection rather than into the blood, accounting for the lack of serum amylase increase. In addition, the remaining functional portion of the pancreas may be incapable of elaborating sufficient enzymes to permit of elevated blood values.

Of importance is the observation that the response of the pancreas to secretin was not impaired, indicating considerable protective and recovery power within the organ following injury.

The radiographic findings were of diagnostic value in identification of the mass. Cysts of the pancreas, if of sufficient density, produce a soft tissue shadow which can be identified by demonstration of their position in relation to surrounding organs. Pseudocysts may be found in relation to the head, body or tail of the pancreas, depending upon which part of the pancreas has been involved in the inflammatory process.

The most common location for pseudocysts is between the stomach and the

liver, which situation is responsible for an extrinsic pressure defect on the lesser curvature of the stomach. They may present between the stomach and the transverse colon, producing a pressure effect on the greater curvature of the stomach and on the upper border of the distal transverse colon. Pseudocysts may be found between the leaves of the transverse mesocolon, in which case signs of pressure will be seen on the distal transverse colon, and only if great enlargement occurs, will the greater curvature of the stomach be indented. A fourth location for pseudocysts of the pancreas is in the mesocolon between the distal transverse and descending colon, and pressure effects will be seen on the lower border of the distal transverse and the medial aspect of the descending colon. In addition the left kidney may be displaced caudad as in the case herein. The location of this pseudocyst was within the gastrohepatic omentum, producing pressure on the lesser curvature of the stomach and the upper border of the distal transverse colon. The retroperitoneal location is indicated by the downward displacement of the left kidney.

Elevation and fixation of the left diaphragm are usually the result of extension of the inflammatory process within the pancreas. Occasionally fluid may be found in the left pleural cavity (4).

A pancreatic pseudocyst may sometimes show calcification within its margins, but this is seen only after the lesion has been present for some length of time, or if it is part of the cycle of chronic pancreatitis with calcification.

Pathology. The pathogenesis of cysts of the pancreas has not been adequately explained by the experimental work thus far reported. Thirolaix (5) was able to produce a cyst of the pancreas by ligating the accessory duct in the dog and injecting 7 cc of a mixture of soot and phenol in petrolatum into the main pancreatic duct. A large cyst was present at the time of sacrifice of the animal three months after the experiment. Clear fluid and small hard irregular calculi were found in the cyst. Lazarus (6) crushed the pancreas in an experiment and sacrificed the animal six weeks later, at which time a cyst was found. Binet and Brocq (7) produced a pseudocyst by injecting calcium chloride into the duct of Wirsung, thereby precipitating acute hemorrhagic pancreatitis.

Pseudocysts of the pancreas are most commonly encountered in association with or following an episode of acute pancreatitis, or following trauma, either accidental or surgical. The differentiation from true cysts rests solely on the demonstration of the presence or absence of epithelium lining the wall of the cyst. A true cyst, being in communication with the pancreas by way of the ductal system will show an epithelial lining. However, if the cyst is of long standing, this layer may be destroyed either by pressure of the fluid or digestion by the activated pancreatic enzymes. It is for this reason that many pathologists feel that attempts at separation of pseudocyst from cysts should be discontinued, but this viewpoint is not generally accepted.

Cysts of the pancreas have been classified on an etiologic basis as follows (8):

1. Cysts resulting from defects in development
 - a) embryonal faults in growth of an acinus or duct
 - b) cysts associated with polycystic disease of the kidney

- c) dermoid cyst
- d) inclusion cysts
- 2. Traumatic—pseudocyst
- 3. Inflammatory—pseudocyst secondary to acute pancreatitis
- 4. Retention cyst—seen in obstruction of the pancreatic duct
- 5. Neoplastic cyst
 - a) cystadenoma
 - b) cystadenocarcinoma
 - c) teratoma
- 6. Parasitic cyst
 - a) echinococcus
 - b) cysticercus
- 7. Cyst seen in cystic fibrosis of the pancreas

The pseudocyst is usually found to be adjacent to rather than within the pancreas and contains fluid within a fibrous tissue wall. The size may vary from a few centimeters to 25 or more centimeters in diameter. Usually the cyst is adherent to the surrounding structures. In most cases the cyst is unilocular, not multilocular, and contains turbid, frequently bloody fluid, or bile. Occasionally a pseudocyst may become secondarily infected thus creating a pancreatic abscess.

Although pancreatic pseudocyst will frequently make its first appearance during the course of acute pancreatitis, as in this case, it is usually discovered in an individual presenting with more chronic complaints, such as upper abdominal pain, digestive distress, anorexia, or constipation. Since these complaints are not pathognomonic of the disease, the diagnosis will be delayed until the appearance of a palpable mass or until X-ray studies suggest the possibility of a lesion in the pancreas. The course is usually progressive with increase in the intensity of the pain and deterioration in health. As the mass enlarges, jaundice, ascites, edema, urinary difficulties and dyspnea may appear with progressive destruction of pancreatic tissue by pressure of the expanding cyst, signs of pancreatic insufficiency will ensue, such as diabetes, steatorrhea and creatorrhea. At this stage differentiation from chronic relapsing pancreatitis may be extremely difficult.

Most cases of pancreatic pseudocyst are detected before these advanced symptoms develop and are invariably subjected to surgery. Palliative procedures, such as aspiration, are of no benefit since the cyst refills soon after the procedure. Some danger is present, since leakage and infection may occur and adjacent hollow viscera may be penetrated by the aspirating needle.

Removal of the pseudocyst is difficult because of adherence to surrounding structures and because of the rich collateral circulation which has developed in association with it. A high mortality, about 25 per cent, has been recorded. The most satisfactory procedure is marsupialization in which the mortality is only about 5 per cent. Anastomosis of the cyst to the stomach or intestine has been reported with some success.

In cases in which the clinical picture improves in association with diminution in size of the mass, a conservative attitude may be adopted and if the mass disappears surgery may be postponed or may even become unnecessary.

SUMMARY

A case of pancreatic pseudocyst in association with acute pancreatitis secondary to alcoholism is described in which the mass developed during the course of the disease. The physical signs and roentgen findings were of diagnostic value, and the usual rise in enzyme values was not encountered. An explanation of this lack of elevation of serum enzyme is offered on the basis of drainage of the pancreatic enzymes into the pseudocyst and their diversion from the blood stream.

The etiologic, pathologic, clinical and therapeutic aspects of pancreatic cysts and pseudocysts are briefly discussed.

REFERENCES

1. RICHMAN, A., AND COLP, R.: Chronic Relapsing Pancreatitis—Treatment by Subtotal Gastrectomy and Vagotomy. *Am. Surg.*, 131: 145, 1950.
2. DREILING, D. A., RICHMAN, A., AND FRADKIN, N. F.: The Role of Alcohol in the Etiology of Pancreatitis. *Gastroenterology*, 21: 636, 1952.
3. HOWARD, J. M., SMITH, A. K., AND PETERS, J. J.: Acute Pancreatitis: Pathways of Enzymes into Blood Stream. *Surgery*, 26: 161, 1949.
4. LIFF, W. F., AND AARON, A. H.: Acute Pancreatitis: Further Observations of Value in its Recognition. *N. Y. State J. Med.*, 50: 2043, 1950.
5. THIROLOIX, J., Quoted by OSER: Diseases of the Pancreas in Nothnagel: *Encyclopedia*. Philadelphia, W. B. Saunders Company, 1903.
6. LAZARUS, B.: Beitrag zur Pathologie und Therapie der Pankreaserkrankungen mit besonderer Berücksichtigung der Cysten und Steine. *Ztscher. f. Klin. Med.*, 51: 95, 1904.
7. BINET, L., AND BROCA, P.: Reproduction expérimentale de la pancréatite hémorragique avec strato-nécrose et du pseudocyste pancréatique par l'injection de sels de calcium dans le canal de Wirsung. *Compt. rend. Soc. du Biol.*, 83: 241, 1926.
8. MAHORNER, H. R., AND MATTSON, J.: The Etiology and Pathology of Cysts of the Pancreas. *Arch. Surg.*, 22: 1018, 1931.

INFLAMMATORY DISEASES OF THE GASTROINTESTINAL TRACT

CLINICAL CONFERENCE*

FREDERICK H. KING, M.D., ALICE I. BERNHEIM, M.D., MARTIN STERNSTEIN, M.D., BURRILL B. CROHN, M.D., RALPH COLP, M.D., ALVIN BAKST, M.D., SAMUEL H. KLEIN, M.D., JOSEPH M. ALPER, M.D., ASHER WINKELSTEIN, M.D., AND DAVID A. DREILING, SR., M.D.

Dr. Frederick H. King: This evening's Clinical Conference is devoted to the matter of inflammatory diseases of the gastro-intestinal tract. In this field, the Staff of the Hospital has, for many years, shown intense and continued interest. As a result, many early, original, and enduring contributions have been made. In introducing the last Clinical Conference, I had occasion to remark that the subject then at hand had evoked only sporadic interest in this Hospital in the past and that interest here had been enhanced by addition to our staff in leading capacities, men from other centers who had a background of prolonged preoccupation with and significant contribution to the subject.

The concept of regional ileitis as a clinical entity was forged here by Dr. Crohn and his associates, Dr. L. Ginzburg and Dr. G. Oppenheimer. This group correlated the clinical and pathological findings and made possible the clinical diagnosis. To Dr. Crohn goes the credit for emphasis and re-emphasis of the clinical symptoms of this and related lesions and their therapy.

For some time now, the pathogenesis of ulcerative colitis has been the subject of investigation by Dr. Alice I. Bernheim and Dr. Abraham Penner. The surgical services under Dr. Garlock and Dr. Colp have added important information to our knowledge of surgical management of these inflammatory diseases.

Among the earliest to call attention to the matter of peptic ulcer of the esophagus and associated peptic esophagitis was Dr. Asher Winkelstein. At this moment, this is the subject of extensive study by a group here consisting of Dr. M. Som, Dr. B. Wolf, and Dr. R. Marshak.

From all this, it is rather clear that we are fortunate, indeed, in having these entities discussed for us by a group so intimately associated with the development of knowledge of these diseases during the past two decades.

The pathological features of ulcerative colitis and regional ileitis will be discussed by Dr. Alice I. Bernheim.

Dr. Alice I. Bernheim: It has been emphasized that the colon has a limited number of modes of response to injury. Various injurious influences produce similar clinical and pathological pictures. In pathology, the term chronic, non-specific, ulcerative colitis relates to the non-specific structural alterations of the colon. These can be of indeterminate origin, or of specific origin, for, in the advanced stages of known specific colitides, the anatomic lesion can simulate the morbid findings of chronic, non-specific, ulcerative colitis of indeterminate origin.

* Held at the Blumenthal Auditorium, The Mount Sinai Hospital, January 21, 1952.

The potential contribution of the pathologist, as well as his definite limitations, to the understanding of the pathogenesis, the healing, and both the operative and natural complications of the disease, are well known. The assorted anatomical and pathological observations collected from clinical and experimental data contribute very little, at the present time, to a real comprehension of the disease. Study of the development of the anatomic lesions emphasizes the fact that even the early changes are non-specific anatomically, and both clinically and experimentally can be elicited by a wide variety of harmful stimuli, not necessarily infectious in nature. In the healing processes, the anatomic definition of inflammatory polypi and their differentiation from true adenomata becomes evident. It is to be noted that inflammatory polypi are not neoplastic, that they are composed of supporting stroma, usually inflamed, covered by surface glands, and that they represent residua and reparative processes and are not tumors. The term polyp of the colon is usually used to signify a polypoid adenoma in which there are polypoid gland proliferations and true neoplasms. Both grossly and microscopically, true adenomata can readily be distinguished from inflammatory polypi although inadequate biopsy material and severe inflammation may render such a distinction difficult. It seems most doubtful if inflammatory polypi could develop into carcinoma. That a relationship between true adenomata and carcinoma exists, is well known. True adenomata are present in a certain number of patients with chronic ulcerative colitis. Whether these adenomata are more liable to malignant degeneration under abnormal conditions of chronic ulcerative colitis is not known to the discussor, although the development of carcinoma is reported to occur in an abnormal frequency in some groups of patients with chronic ulcerative colitis, especially those with longstanding disease, in the younger age groups. The difficulty in distinguishing pathologically between certain cases of familial polyposis accompanied by diffuse ulceration and cases of chronic ulcerative colitis with adenomatous polypi is appreciated by most pathologists.

The pathology of regional ileitis is quite distinct from that of ulcerative colitis. Emphasis must be placed on the fact that a certain number of patients with regional ileitis develop lesions high in the small bowel after short circuiting operations with exclusion or excision of the diseased areas. It is felt that many, if not most, of these lesions could have been present from the onset. This impression is based on the fact that previously unsuspected lesions of very minute size are seen in areas of specimens resected wide of clinically obvious disease.

CASE 1. REGIONAL ILEITIS

Dr. Martin Sternstein: This patient, a 28 year old married woman, was first admitted to Mount Sinai Hospital in March 1951. At that time, she stated that she had had generalized abdominal cramps and constipation since the age of 19. During one acute episode of these cramping pains, she was seen by a physician and the diagnosis of acute appendicitis was made. The patient underwent an appendectomy. This was in 1941. She recalls that the drains were left in the wound, then removed, and subsequently replaced for several months.

Seven months after this operation, she developed nausea and vomiting and lost about

twenty pounds in several months. She was admitted to the Presbyterian Hospital, where, after several studies were made, a resection of the ileum was performed. This was in 1943. She regained her lost weight but continued to have non-bloody bowel movements, two of them a day, containing mucous, for several months postoperatively.

In 1947, during and for some time after a pregnancy she complained of anorexia, loss of weight, frequent episodes of abdominal cramps and, again, had two to four loose bowel movements per day.

At one time, she refused to undergo a vagotomy which was suggested. In 1948, she went to another physician who took barium enemas and told the patient that she had ulcerative colitis. He placed her on a diet and gave her injection. She got moderate relief and, in a seven month period after this, she gained ten to fifteen pounds. She was then well for the next ten months.

In March of 1950, her symptoms reappeared, with this she developed an intermittent fever. She was hospitalized at a Bronx Hospital in May 1950, where a fecal fistulous tract was discovered for the first time. The patient was treated with intravenous feedings, transfusions, and antibiotics. She improved slightly after four weeks, but, in the fifth week, the fistula started draining again. The patient consulted another physician who, at this time, advised surgery. However, the patient preferred to return to another hospital for further symptomatic treatment. Prior to admission, she had occasional episodes of diarrhea without gross blood. Her febrile course had continued and her fistula tract drainage had persisted.

X-rays taken one week before admission to this hospital showed evidence of recurrent granulomatous ileitis with narrowing at the stoma of previous ileo-transverse colostomy. There were intercommunicating fistulae at the area of narrowing.

Physical examination on admission revealed the temperature to be normal but soon afterwards she developed a low-grade fever. Pulse, respiration, and blood pressure were all normal. She was very thin and appeared undernourished but was not acutely ill. Positive findings centered about the abdomen. There was a transverse scar in the right upper quadrant and a McBurney scar in the right lower quadrant. At the upper end of the McBurney incision there was a fecal fistulous tract with two openings. The tract could be probed for about two inches. Pelvic and rectal examinations were negative.

Laboratory studies revealed a trace of albumin in the urine with three to four white blood cells. The hemoglobin was 10.5 grams. The white blood count was 22,000. The total blood protein was 6.5 grams percent with 2.6 albumin and 3.9 globulin. The stool guaiac test was 2 plus. Blood cultures were negative.

Course: For two weeks, the patient was given a high protein, high caloric diet, blood transfusion, and supplemental vitamins. Thirteen days after admission, following preparation with sulfasuxidine, she underwent an ileotransverse colostomy with exclusion and exteriorization of the proximal colon. The postoperative course was uneventful. There was minimal drainage from the fistulous tract. The patient was discharged thirteen days postoperatively to return at a later date for possible excision of the excluded bowel.

The pathological report of the surgical specimen removed at time of ileotransverse colostomy showed it to be a small fragment of the small bowel wall displaying acute and chronic inflammation in the submucosa.

The patient was seen in the follow-up clinic in April and had gained fifteen pounds. The fistulae had closed. In July, she complained of mild cramps but had no disturbance of bowel function. The patient was readmitted in November of this past year with a history of having developed an upper respiratory infection eight weeks before coming back to the hospital. She had a cough productive of green mucoid sputum and intermittent fever. With the respiratory infection she had lost ten pounds in eight weeks, although before this she had gained approximately fifty pounds. The patient also complained of an increase in the bowel movements to three or four loose stools per day. The stools were without blood and without mucous.

On the second admission in November, the temperature was 100. Her pulse, respira-

tion, and blood pressure were again normal. The spleen and liver were both palpable one finger below the costal margin and were non-tender. The colostomy appeared healthy although there was a slight mucous discharge present. The wounds were all healed. Laboratory investigations at this time revealed total protein 6.4 gram; hemoglobin 13.1 gram; white blood count 6500; and urine normal. An examination with barium on the second admission showed the ileum, at the site of anastomosis and extending approximately for several feet proximally, to be the site of inflammatory change with thickening of mucosa and irregularity of the bowel lumen. There was no evidence of stricture.

The patient was discharged shortly after the X-rays were taken, without surgery, since it was felt that the symptoms were not severe despite the presence of active disease.

Dr. Burrill B. Crohn: This is an unfortunate case. Even though the illness was recognized fairly early, the operative procedures did not succeed in effecting cure of the disease. You notice that the woman is 28 years of age now and that the disease began about 10 years ago when she was 19 years of age. The onset with so-called appendicitis was very insidious and for ten years she had an illness which practically was unrecognized. Fortunately, when the appendectomy was performed, she did not develop a fecal fistula. That would have been even more disastrous. The long intermission periods from the very beginning of the first symptoms to the onset of the other conditions are very intriguing. The appendectomy may precede the onset of diarrhea and other symptoms by very many years. Indeed about 25% of the early cases, at the time when the diagnosis is first made, have already had appendectomies.

Now, this woman was operated on and resection was performed. Our experience is that resection has no advantage over the exclusion operations. Dr. Colp will probably develop that subject. In our hospital, it is an unusual matter to have resections performed. As I often say jokingly, had I studied ileitis now instead of the early days, I would never have been able to see pathological specimens and would never have been able to formulate a true concept of the pathology of the disease. Nowadays, with the short-circuiting operation, one rarely sees a gross specimen of ileitis.

This woman unfortunately had a resection and very shortly thereafter she had a recurrence of disease. These recurrences take place in, we will say, anywhere between 15% and 22%. The revised figure of today is 22%. Most of these recurrences take place, not immediately after the operation, as in this case, but rather in five years, two years, seven years, nine, fourteen, and, I have seen one case in which the recurrence took place seventeen years after the original operation.

I would like you to bear in mind that when it comes to attempting to develop the etiology of this disease, one cannot conceive of bacteria lying dormant for fourteen or seventeen years and then coming to life again. It is true that tuberculosis can do it. But there are very few infectious diseases, bacterial or viral, that would allow a patient to remain well for so many years before the recrudescence takes place.

My attitude as to these recurrences is a very conservative one. They do not lend themselves, most of the time, to surgical therapy. Unfortunately, the disease cannot be cured by anything that we have at hand today, including anti-

biotics or hormone therapy. Yet, mild recurrence proximal to the lesion can be treated conservatively, and need not necessarily, when the diagnosis is made, lead to panic and immediate demand for surgery. On the contrary, it is much better to treat these conservatively with what we have on hand to carry them along.

Now when you get a malignant type of ileitis, such as this, where the recurrence is so great that it threatens to move upwards, then it is necessary, particularly with the formation of a fecal fistula, to operate. Here there is some difference of opinion which I would like Dr. Colp to elucidate. Some people, in doing the second ileo-transverse colostomy, will resect completely the diseased area proximal to the new anastomosis, while others, and I think Dr. Colp is one, will leave the lesion in and merely exclude it. There is some evidence that it is not always necessary to remove the segment. If left alone, it will, as the first ileitis, atrophy and wither.

The second operation was done in this case and, unfortunately, this woman has gone on, now, to a stage of recurrence of ileitis in which almost the whole small intestine is involved, even up to the duodenum. Now, the colon might be expected to be the seat of recurrence but this has not been proved, as far as I know, from the description of the case. Indeed, in spite of the fact that almost the whole small intestine is involved, the colon seems free of disease. While this appears to be the rule, there are too many exceptions for comfort. In case after case, one sees the recurrence takes place not only in the entire proximal ileum but also in the colon, sometimes all the way down the colon to the rectum. Fortunately, the latter cases are unusual. The natural immunity of the colon to the disease in the small intestine is inexplicable.

When one sees a case of this kind in which the recurrences involve the whole jejunum with fistula formation, one is faced with a very serious and difficult therapeutic problem. The problem becomes even more acute if the patient develops electrolyte imbalance with tetany, hypoproteinemia with peripheral edema, iritis, arthritis, dermatitis, or phagedenic necrosis of the skin.

Vagotomy is an extreme measure. I have not seen much of vagotomy, but in the two cases in private practice which I saw, both died in spite of the vagotomy. I do not think vagotomy is the answer to this problem at all. Dr. Hinton has tried sympathectomies and pelvic section of the parasympathetic fibers as well, but these procedures are still experimental.

There was just one remark that Dr. Bernheim made which bothers me a great deal. Dr. Bernheim said that the specimen of ileum, which is sometimes removed by the surgeon at the point of anastomosis, frequently shows disease. It was my impression that this biopsy practically always came back negative and that the judgement of the surgeon in choosing the site of transection was justified in most cases. Dr. Bernheim seemed to drop a hint that some of these specimens show acute and chronic inflammation. If that is so, then the possibility of choosing the healthy part of the ileum for the anastomosis seems pretty hopeless. Some have suggested that ileitis is a disease of the whole small intestine *de nova* and that when we see the clinical picture at operation, we see only that

part of the small intestine in which the disease settles down and becomes residual. The remainder of the small intestine presumably frees itself of the noxious agent, whatever it is. If this concept is true, it must be obviously very difficult, if not impossible, for the surgeon to pick and make his anastomosis in bowel which is free of disease.

Dr. Ralph Colp: Dr. Crohn is so in the habit of telling surgeons what to do that he has told me what to discuss. So, in accordance with the mandate which I have received from him, I will devote the few minutes at my disposal to a discussion of recurrence of ileitis.

I think Dr. Ginzburg was absolutely right when he called to my attention the fact that most cases of recurrent ileitis were really a persistence or a progression of an ileitis that was present at the time of the anastomosis. I also think that Dr. Bernheim was absolutely right in making a statement that she had received pieces of small intestine which were taken at the site of the anastomosis in an area in which the surgeon was under the impression that he was operating on normal bowel. These specimens though macroscopically normal, microscopically showed submucosal inflammation and mucosal ulceration. It has been my routine procedure to remove such specimens. In some cases, much to my chagrin, the patient, at the time she or he left the operating room, already had a progression of the disease for which I had originally operated.

In the twenty years which have gone by, we all have come to know that there are cases of ileitis confined to the terminal ileum which we mistakenly operate upon for acute appendicitis. Nothing is done for these patients and many of them recover without any further difficulty. We also know that there are cases of diffuse jejuno-ileitis which have been explored and which, at the time of operation, have presented such extensive involvement that nothing could be done except closure. Several of these patients have returned at subsequent dates with no symptoms and with normal bowel X-rays. In our experience, the best results obtained in the surgery of ileitis, are those in which the disease apparently seems localized in the terminal ileum.

In 1934, Dr. Ginzburg and myself, in order to diminish the mortality of resection for ileitis, started doing a two-stage procedure. We found that many of these patients recovered, that their fistulae disappeared, and that even their abscesses resorbed. Therefore, we felt that we could adopt a side-tracking procedure with ileal division as a definitive measure. The procedure which was initiated at that time is the operation of choice at the present time.

Dr. David A. Dreiling and I have recently reviewed the literature concerning recurrence following surgery for ileitis. The recurrence rate runs as high as 57% in some series. Amongst 2,209 cases of ileitis treated by resection, the average recurrence percentage was 21.9 and the mortality rate was 11.2%. A similar series of 782 patients with ileitis treated by ileocolostomy with exclusion exhibited a recurrence rate of 28.9% and a mortality of 4.6%. Now I think this emphasizes two things. The percentage of recurrence has very little to do with whether a resection is performed or whether an exclusion is done because in the majority of the cases recrudescence occurs in the proximal ileum. In those instances in

which you resect at a second stage, many of the lesions are already healed. There are, however, rare cases in which the disease is not quiescent in the ileum which has been excluded and in these instances you may get fistulae. These rare cases cannot be taken as an indictment of the operation of ileocolostomy with exclusion because of the low mortality of that operation compared with the mortality for the resection procedures. After all, that is an important consideration.

I feel reasonably sure that the longer cases of ileitis are followed, the greater will be the percentage of recurrence. In the present state of our knowledge, we are operating on these patients only when our hand is forced by intestinal obstruction, fistulae, and abscess formation. As Dr. Crohn said, I think we are becoming much more conservative in treating patients with a simple diarrhea even though the X-ray shows ileitis.

I thought it would be interesting to review 10 cases of recurrent ileitis treated surgically because of complications. In the secondary operation, rather than going through the ordeal of resecting diseased bowel, and transverse colon, I have been in the habit of leaving the bowel attached to the colon and performing an ileal division with ileosigmoidostomy. These patients are summarized in Table 1.

Now you can see from the primary operations that persistent disease follows both resections and side-tracking operations. The interval of time that has elapsed between the first operation and the second varies tremendously. Here is a patient (#2) who had an ileocecal resection in two stages and was well for five years. Following an ileal division with ileosigmoidostomy, the patient has remained well for eight years. Here is a woman (#4) who had a recurrence within six months of her primary operation and who had an ileal division with an ileosigmoidostomy. At the end of five years, there is a secondary recurrence which is being treated conservatively because of lack of clinical symptoms. Here is another patient (#5) who developed a recurrence nine years later and who has been well for five years following a secondary exclusion. Patient #6 was well for two years following the primary operation. An ileal division with ileosigmoidostomy has brought relief for four years. Here is a patient (#9) who had a two stage ileocecal resection with ileosigmoidostomy and then had an ileal division with another ileosigmoidostomy. She remained well for fourteen years after which it became necessary to remove the excluded bowel in which active disease had persisted. The last patient (#10) had an ileosigmoidostomy with exclusion, was well for twelve years, and then developed symptoms which necessitated an ileocecal resection. Thereafter she remained well for three years, following which proximal recurrence was discovered by X-ray. This patient is being treated conservatively because we feel that there must be a reason for operation, either signs of intestinal obstruction, abscess, or fistula formation.

The mortality of secondary exclusion is definitely lower than for resection. If you get a recurrence which follows the pattern of the original disease, I think it is far safer to do another ileal division as far away from the lesion as possible. We have recommended going 60 cm. from the last definite signs of a skip area.

TABLE 1

Ten Cases of Proximal Recurrent Ileitis Treated by Secondary Ileal Division

CASE AND SEX	PRIMARY OPERATION	INTERVAL BETWEEN FIRST AND SECOND OPERATION	SECONDARY OPERATION	PERIOD OF FOLLOW-UP AFTER SECOND OPERATION	PRESENT STATUS
		<i>Yr.</i>		<i>Yr.</i>	
1 Male	Ileocecal resection, ileotransverse colostomy	5	Ileal division with ileosigmoidostomy	2½	Died*
2 Female	Ileocecal resection two-stage, with ileotransverse colostomy	5	Ileal division with ileosigmoidostomy	8	Well
3 Male	Ileocecal resection, ileotransverse colostomy	1½	Ileal division with ileosigmoidostomy	6	Well
4 Female	Ileotransverse colostomy with exclusion	½	Ileal division with ileosigmoidostomy	5	Secondary recurrence†
5 Female	Ileocecal resection, ileotransverse colostomy	9	Ileal division with ileosigmoidostomy	5	Well
6 Male	Ileotransverse colostomy with exclusion	2	Ileal division with ileosigmoidostomy	4	Well
7 Male	Ileocecal resection, two-stage, with ileotransverse colostomy	6	Ileal division with ileosigmoidostomy	3½	Well
8 Male	Ileocecal obstructive resection	1	Ileal division with ileotransverse colostomy	7	Well
9 Male	Ileocecal resection, two-stage, with ileosigmoidostomy	14	Ileal division with ileosigmoidostomy	5	Well
10 Female	Ileosigmoidostomy with exclusion	12	Ileocolic resection	3	Well;‡ proximal recurrence

* Patient died of an acute intestinal obstruction. No evidence of recurrent disease.

† Abdomen was explored after 18 months because of diarrhea and weight loss. The excluded ileum was found to be healed and restored to intestinal activity. Abdomen was reexplored five months later for intestinal obstruction. A tertiary ileotransverse colostomy excluding the secondary recurrence was performed.

‡ The patient is clinically well, but x-ray evidence of proximal recurrent ileitis is present.

If you do that, many of these patients will not only remain well, but we now know from X-ray and from secondary operation, that the loop of bowel which has been left connected with the transverse colon will heal just as the terminal ileum healed in the original procedure.

ULCERATIVE COLITIS

Dr. Alvin Bakst: I shall take this opportunity to present two cases of ulcerative colitis.

The first case is that of an 18 year old girl who was first admitted to the Psychiatric division of this hospital for ulcerative colitis of six months duration. She entered the hospital complaining of diarrhea, abdominal pains, elevated temperature to 102°, a rash over both lower legs, and polyarthritis involving the left elbow, wrists, and ankles.

Examination: The patient had polyarthritis, erythema nodosa, and, in addition, she had bilateral catarrhal conjunctivitis. The laboratory workup included stool examination for parasites which was negative. The erythrocyte sedimentation rate was approximately 82 mm per hour. X-ray studies of the colon revealed a diffuse ulcerative colitis from the hepatic flexure to the sigmoid. Sigmoidoscopy was negative. The patient continued to run fever and continued to have diarrhea despite psychotherapy and routine medical conservative therapy. Consequently a course of ACTH was instituted. The patient received 60 milligrams of ACTH daily for one month.

Almost immediately after receiving ACTH, her temperature returned to normal, the arthritis disappeared and the conjunctivitis cleared. She felt generally better. Upon termination of the ACTH therapy at the end of the month, however, every sign and every symptom promptly returned. She was treated expectantly for a few weeks following which a course of cortisone was started. This was continued for six weeks. Again all the symptoms disappeared but when the cortisone was stopped there was a recrudescence of illness.

After further treatment with ACTH and cortisone, another barium enema was done. These X-rays showed progression of the disease to the involvement of the entire colon. Sigmoidoscopy was repeated. The anal canal was now the seat of a diffuse ulcerative colitis with active ulceration and bleeding. The progression of the disease despite therapy made surgery mandatory. An ileostomy and subtotal colectomy in one stage was performed. The patient's response has been gratifying. She has gained 30 pounds since operation.

The second case is a 29 year old man who had even more psychotherapy for his disease. He was treated for six years. The patient entered the hospital with a ten week history of diarrhea, weight loss, fever, and rash over both lower legs. He was first seen in this hospital in 1943 at which time the diagnosis of ulcerative colitis was made. Psychotherapy was advised and instituted at that time. Except for periodic relapses he did fairly well on medical and psychiatric therapy. However, 10 weeks prior to admission he became acutely ill with high temperature and increase of bowel movements up to twenty per day.

Examination: The patient was acutely ill and markedly disturbed. Barium enema showed extensive ulcerative colitis throughout the colon with foreshortening, rigidity, and pseudopolypoid changes. Sigmoidoscopy confirmed the presence of extensive severe disease. An ileostomy was performed. At first the patient began to gain weight and felt well. On the twentieth postoperative day, however, he began to pass blood per rectum. He continued to bleed profusely despite repeated transfusion. Repeat sigmoidoscopy showed a friable congested mucosa which bled freely. To control this blood loss, one month after ileostomy, a subtotal colectomy was performed. Since this second operation the patient has continued to do well and has gained forty pounds.

Dr. Samuel H. Klein: These two patients fortunately display marked improvement as the result of surgical intervention.

As you know, ulcerative colitis is a disease of no known cause. We have attempted to study this disease intensively at this hospital by a system of teamwork between the psychiatric, medical, and surgical services.

I would like to emphasize at the beginning that ulcerative colitis is by no means entirely a surgical disease. As a matter of fact, it is, by and large, a

medical disease. Between 80% and 95% of the patients can be treated adequately and get along quite well by means of medical and psychiatric care.

I think it is also generally conceded that psychiatric influences play a great role in the disease. Whether this role is active not only in the initiation of the disease but also in the development and progression, cannot be conclusively stated at this time. It has been our experience that psychiatry has been of great help in caring for these patients.

Medical therapy, of course, has been invaluable throughout all phases of treatment of ulcerative colitis. Yet despite medical and psychiatric therapy, in some patients the disease progresses to produce the pathological changes that were so beautifully portrayed by Dr. Bernheim. When this has occurred, it is difficult to understand in what way further medical and psychiatric therapy can benefit the patient or bring about reversal of the pathological changes. These patients, with severe progressive lesions, constituting about 15% of all cases of ulcerative colitis, are those in which surgery is required.

Clinically, the surgical cases fall into two main groups. These are the fulminating cases and the chronic cases. Of course, there are gradations between the two. The fulminating cases are manifested by fever, prostration, toxemia, sometimes hemorrhage, marked diarrhea, and so forth. The chronic cases present invalidism, recurrent fever, persistent weight loss, abdominal pain, skin changes, and joint disorders.

Once patients have reached either the fulminating stage or the chronic stage with invalidism, we feel they are surgical. Persistent psychiatry in these cases may be unwise. We have seen a fair number of cases, now, in which psychiatric treatment has been continued after a recommendation was made that surgery be done. These patients have not done well. In some cases we feel that the optimum point for operation was missed.

We also feel that once the decision has been made to operate, the problem should be discussed frankly and honestly with the patient. We have been called in on many cases and asked not to discuss surgery and the surgical aspects of the condition for fear of upsetting the patient. In our experience the best results are obtained when we discuss the problem frankly with the patient, explain the nature of the disease, and explain the nature of the procedure to be done. We find that when we can create a sympathetic understanding between patient and surgeon, when the patient has made a transference to the surgeon, as he did originally to the psychiatrist, and when he understands what is to be done and the reasons for these things, we are much more successful in rehabilitation of the patient.

We have an ileostomy club where these people meet and where they discuss their personal problems with regard to their ileostomies. Many of these people have been returned to economic and social usefulness. Some of the men have married and some of the women too. They have had children and have reared families and have adjusted very well to ileostomy.

I should like to make one further remark, and that is about carcinoma. Dr. Bernheim has stated that the pathologists have been unable to show a definite

relationship between the so-called pseudo-polypi and the development of carcinoma. We cannot take issue with this point. However, it has been the surgeons' impression that there is a greater incidence of carcinoma in patients with long-standing ulcerative colitis than one would expect statistically. These colonic carcinomas occur in young people and progress with tremendous rapidity. Sometimes the patients are dead a few weeks after the diagnosis of malignant tumor has been made.

PEPTIC ESOPHAGITIS

Dr. Joseph M. Alper: We shall present four cases of peptic esophagitis. The material to be shown will illustrate some of the interesting clinical and therapeutic features of the disease.

The first case emphasizes an unusual complication of peptic esophagitis. The patient is a 58 year old man who had a fifteen year history of duodenal ulcer. During this time he had one perforation and one massive hemorrhage. For six months prior to hospitalization, there were severe ulcer symptoms which were refractory to the usual medical therapy. One month before hospitalization, the patient complained of dysphagia and pain under the sternum. He was able to swallow liquids only. X-ray examination revealed peptic esophagitis, a small hiatus hernia, and, in addition, a small duodenal ulcer. Operation was refused. The patient improved under conservative therapy, was able to take soft foods, and went home. One month later, the patient had another perforation of his duodenal ulcer. The perforation was repaired within six hours after its occurrence. Two days post-operatively, the patient complained of a sudden severe substernal pain, went into shock, and died ten hours later. Autopsy revealed peptic esophagitis and a perforated ulcer in a portion of the stomach which had herniated into the chest. The rare complication in this case was the perforation just below the area of peptic esophagitis.

The second case is that of a 45 year old man who gave a history of heartburn and severe postprandial and nocturnal epigastric pain. His symptoms were of one year's duration and were not relieved by milk nor antacids. On the basis of X-ray examination, esophagoscopy with biopsy, a diagnosis of peptic esophagitis was made. The patient was given a bland diet and anti-spasmodics. He was very well for a period of three years following which he began to have dysphagia to solid foods and the occasional regurgitation of undigested matter. X-ray examination revealed a stenosis of the lower third of the esophagus with a slight dilatation above the constricted area. Esophagoscopy confirmed this and biopsy disclosed benign inflammation. Treatment with a mercury weighted bougie was advised and has been used by the patient with complete remission of symptoms for the past nine months. This case illustrates the isolated occurrence of peptic esophagitis and a good result of dilatation therapy.

The third case is that of a 45 year old police officer who had a three year history of increasing dysphagia and occasional regurgitation of unchanged food. X-rays and esophagoscopy revealed esophagitis. In November 1950, he was admitted to the hospital and was operated upon by Dr. Garlock. The lower portion of the esophagus was buried in adhesions. A bilateral vagotomy was performed. There was some improvement for a period of two months. Then the patient suffered a relapse of symptoms. He did not respond to ulcer therapy. Esophagoscopy by Dr. Max L. Som revealed superficial ulceration of the mucosa and some narrowing of the lumen of the esophagus. The biopsy report showed acute inflammation. Gradual dilatation of the esophagus was instituted. The patient has returned at intervals of four weeks for this treatment. He has been free of symptoms on this therapy and his most recent X-ray was reported as showing no abnormality of the esophagus, stomach, nor duodenum. This case shows good results with dilatation.

The fourth case is that of a 66 year old white man who was hospitalized in March 1951

because of substernal pain, dysphagia, and a loss of weight of twelve pounds during a period of eight months. X-ray examination revealed dilatation of the proximal two-thirds and a narrowing of the distal third of the esophagus with an ulcer of the anterior aspect of the narrowed portion of the esophagus. Esophagoscopy and biopsy confirmed the presence of peptic esophagitis. Dilatation of the constricted section was begun with relief of the patient's symptoms. There was one episode of slight gastric hemorrhage after the dilatation was begun. The patient was rehospitalized. X-ray examination on this occasion revealed that the esophageal lesion had decreased in severity. However, a duodenal ulcer could now be demonstrated. Surgery was contraindicated because of arteriosclerotic heart disease. The patient has been maintained on a bland diet with periodic dilatations. He has done well. This case illustrates the good result of dilatation and the subsequent development of a duodenal ulcer in a patient with peptic esophagitis.

Dr. Asher Winkelstein: In the early 1930's, I encountered a group of elderly male patients who had dysphagia, substernal pain on swallowing, and emaciation. X-rays were reported as being strongly suggestive of a carcinoma of the lower end of the esophagus. That group of patients was esophagoscoped by Dr. Rudolph Kramer. He described the lower third of the esophagus as showing gradual narrowing with a patchy gray exudate covering an inflamed mucosa. Biopsies showed acute inflammation of the mucosa and submucosa. It was then noted in this group of patients that there was a history of duodenal ulcer, gastric ulcer, jejunal ulcer, or that these patients subsequently developed a peptic ulcer. These early cases were not associated with hiatus hernia. Because of definite association with peptic ulcer, I entitled this group peptic esophagitis. The series of cases was presented at the American Medical Association meeting in Cleveland in 1934 as a new clinical entity whose greatest significance was in the differential diagnosis of carcinoma of the esophagus.

Since then, many cases have been reported in the literature, some under the title of peptic esophagitis, some under the title of stenosing esophagitis, and some even as spasm of the lower esophagus. There are apparently several groups of cases which should be separated. There is one group which I have just described to you in which the esophagitis occurs alone or in association with peptic ulcer elsewhere. The second group of peptic esophagitis is related to or results from a hiatus hernia or a congenitally shortened esophagus. Then there is a third group in which the esophagitis follows anastomotic operations as is necessary in gastrectomies and in surgery for cardiaspasm.

The etiology of the group of cases, which is associated with a previous ulcer or in which an ulcer develops later, is probably the reflux of acid peptic secretion from the stomach back into the esophagus. This, in patients who are predisposed to ulcer, leads to peptic esophagitis. In some rare cases, peptic esophagitis may be due to the presence of ectopic gastric secretory mucosa in the esophagus.

In most of these patients, the ordinary medical therapy suffices. However, some go on to develop very serious symptomatology. They have severe dysphagia, substernal pain; some have bleeding and some develop the worst complication of all, stenosis. In most cases mechanical dilatation seems to give very satisfactory results. In three of the four cases presented by Dr. Alper, you saw

the excellent results with mechanical dilatation. However, there are some cases which do not respond, and in these, surgery is necessary. The question of the proper surgical therapy of this disease is, at present, in a state of flux. Subtotal gastrectomy has been advocated and carried out by Dr. Wangenstein. Dr. Colp has done a number of cases here also. Vagotomy, as you have heard, has been tried in a few cases. Esophago-gastrectomy was tried in a fair series in Boston. All of these surgical procedures are more or less successful.

Before closing, I would like to point out that despite the similarity in etiology, peptic ulcer of the esophagus and peptic esophagitis are two different conditions. Ulcer is a sharply localized circumscribed lesion, as you have seen, whereas esophagitis is a diffuse lesion. Ulcer penetrates and perforates; esophagitis does not. Both of them, however, may stenose and both of them may bleed.

Dr. Max L. Som: An endoscopist ordinarily doesn't get to see cases of peptic esophagitis until there has developed an obstructive lesion of the esophagus. Occasionally patients with peptic esophagitis are referred to the endoscopist because of the suspicion of carcinoma or because X-ray examination has shown a thoracic stomach. On such occasions, the endoscopist has the opportunity of directly visualizing the esophagus and the thoracic portion of the stomach in the earlier stages of the disease.

The cases of esophagitis that our group has studied have all been associated with a thoracic stomach or with a hiatus hernia. The first patient I had occasion to see was a man in the late 60's who during a routine X-ray examination of the digestive tract was found to have a thoracic stomach. He was referred for esophagoscopy because there was a possibility of an intrinsic lesion of the esophagus. It was found that the gastro-esophageal juncture was at 35 cm. from the incisors. This is five centimeters above the position that we would expect in a normal adult. The esophageal mucosa of this patient appeared normal and there was no evidence of peptic esophagitis. The patient was reassured. Some four years later, he came back with symptoms of heartburn and dysphagia. This time on esophagoscopy, there was a superficial ulceration of the lower portion of the esophagus. The cardia-esophageal juncture was incompetent. The escape of gastric contents into the upper esophagus could be visualized before the scope was passed into the stomach. In other words, there was gastric reflux. As a reaction to this reflux, there had developed esophagitis. This is the causal relationship between hiatus hernia and esophagitis. The hiatus hernia, per se, may be asymptomatic. Yet when incompetence of the esophago-gastric juncture supervenes, gastric reflux follows. The result of gastric reflux is peptic esophagitis.

The clinical picture of peptic esophagitis appears to be divided into two phases. In the early non-obstructive phase there is inflammation and symptoms of dyspepsia and heartburn. In the later phases there is healing with scarring, stenosis, and esophageal obstruction of varying degrees. This is the stage at which the endoscopist is most likely to see patients with peptic esophagitis. We dilate the stenotic areas even though we believe the condition itself is due to incompetence of the cardia-esophageal juncture. After dilatation the symptoms

of obstruction usually disappear and the symptom heartburn responds to medical therapy.

In advanced cases of peptic esophagitis the area of stenosis may be quite extensive and involve almost all of the thoracic esophagus. In these patients, the esophago-gastric juncture, as indicated by esophagoscopy measurements and biopsies, may appear high above the diaphragmatic hiatus. This poses the question as to whether such a position is due to gradual retraction of the stomach into the thorax or whether a hiatus hernia with thoracic stomach is always present in these individuals. In one particular patient whom we have studied repeatedly over a period of nine years, the answer is definite. When this patient first presented himself, the esophago-gastric juncture was at 35 cm. at which point there was an ulceration. The patient was treated with dilatation with some relief of complaints. He returned for esophagoscopy, dilatation, and biopsy over the nine year period of observation. Biopsies and measurements during this time have shown that the esophago-gastric juncture has been pulled up into the thoracic cage. At the last esophagoscopy, a few months ago, the level was at 25 cm. Below this a biopsy showed gastric mucosa. In other words, in this patient, the esophago-gastric juncture has been pulled into the chest at least 10 cm.

From the pathological point of view this process is understandable. The esophagus is anchored at the thyroid cartilage and the thyroid cartilage is fixed in the neck. Thus in the pathological development of peptic esophagitis, when the healing processes begin, any contraction of the esophagus due to scar formation in the submucosa must tend to pull the stomach up into the chest.

After the stenotic phase of the disease has been reached, the patient may go on to a spontaneous cure in the development of a stricture. If you esophagoscope such a patient, you will find a dilated esophagus without any evidence of inflammation or ulceration and, of course, a stricture. In some there may be a chronic non-specific esophagitis due to retention.

In summary, we believe peptic esophagitis associated with hiatal hernia is due to gastric reflux. It occurs in older people who have had asymptomatic hiatus hernias when they develop incompetence of the gastroesophageal juncture. The reflux of acid from the stomach causes the esophagitis. The disease goes through a cycle of inflammation followed by healing with stenosis, contraction, and even shortening of the esophagus. During this process the esophago-gastric juncture may be gradually drawn up into the thoracic cage.

ABSTRACTS

AUTHOR'S ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out patient department of the Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

Electrokymographic Studies of the Normal Cardiac Cycle. H. MEDNICK, J. B. SCHENDEL, AND P. SAMET. *Circulation*, 2: 250, August, 1950.

The electrokymogram is an instrument for the recording of cardiac border motions. A multiplier phototube, with a Patterson type B fluorescent screen placed over the window of the phototube, is located on the back of a fluoroscope, preferably with full-wave rectification. As the heart contracts in systole and expands in diastole more and less roentgen ray energy penetrates to the phototube. This variation is translated into electrical energy by a special filter circuit and characteristic curves of border motion can be recorded from within the heart itself. This paper deals with the normal electrokymogram. The duration of the various phases of the cardiac cycle as recorded on the left ventricular electrokymogram is listed.

Longitudinal Growth of the Human Vertebra. E. M. BICK. *J. Bone & Joint Surg.*, 32A: 803, October, 1950.

Longitudinal growth of the vertebral body takes place by means of true epiphyseal cartilage plates as does the longitudinal growth in the metaphysis of long bones. The vertebral ring, often observed in the roentgenograms of growing vertebrae, is an apophysis rather than epiphysis and takes no part in the longitudinal growth of the vertebral body.

The Combined Use of Picrotoxin and Amphetamine (Benzedrine) Sulfate in Barbiturate Intoxication. B. W. BILLOW. *Am. Pract.*, 1: 1009, October, 1950.

Statistics reveal a widespread increase in the use of barbiturate derivatives and the resultant rise in the number of poisonings, intentional or accidental. The diagnosis of barbiturate poisoning is apt to be difficult. Coma, with shallow, rapid respiration, contracted pupils, absence or diminished reflexes, and feeble and rapid pulse, should suggest the possibility of barbiturate poisoning. The aim of the treatment is to combat the action of the drug by antagonistic drugs and supportive therapy and to prevent secondary complications such as pulmonary congestion, pneumonia and coronary insufficiency. The author presents in detail a therapeutic regimen used successfully in 12 cases during the past 3 years. Picrotoxin and amphetamine are used as antagonistic drugs in this regimen. It is important to be on the lookout for the rather common manifestations of picrotoxin toxicity, such as diarrhea, vomiting, bradycardia and sweating. With the treatment described, there were no deaths and no severe reactions.

Dextrorotary Acids of Tubercle Bacilli Lipids. J. D. CHANLEY AND N. POLGAR. *Nature*, 166: 693, October, 1950.

This is a preliminary report on the dextrorotatory acids of the lipids of human tubercle bacilli, hitherto believed to be saturated acids. During his work in Robinson's laboratory in Oxford, Dr. Chanley found that these acids are α,β -unsaturated. This finding requires a complete revision of current concepts concerning the lipids of acidfast microorganisms.

Multiple Myeloma: Lesions of the Extraosseous Hematopoietic System. J. CHURG AND A. J. GORDON. Am. J. Clin. Path., 20: 934, October, 1950.

In 44 consecutive cases of multiple myeloma which came to autopsy at the Mount Sinai Hospital between the years 1933 and 1950, 31 (or 70 per cent) showed myelomatous infiltration of the extraosseous hematopoietic system (spleen, lymph nodes and liver). In 14 instances this involvement was recognizable on gross examination. Microscopically, the usual pattern of visceral lesions was similar to that seen in the bone marrow, namely diffuse infiltration with more or less tendency to nodular aggregates. These findings support the idea that multiple myeloma is a disease of the hematopoietic system closely allied to leukemia, though concerned with a separate cell type, the plasma cell.

Collagen Content of Guinea Pig Tissues. S. K. ELSTER AND E. L. LOWRY. Proc. Soc. Exper. Biol. & Med., 75: 127, October, 1950.

1. Chemical measurements were made of the collagen content of the lungs, liver, kidneys, spleen, heart and skeletal muscle of 58 guinea pigs weighing between 60 and 1000 g. 2. The concentration of connective tissue components varied with different tissues; the lungs contained the greatest proportion, and the liver the least proportion, of collagen. 3. Tissues from older animals usually contained a higher per cent collagen than comparable younger tissues, except for the spleen where the converse was true. 4. The values obtained for guinea pig tissues were in essential agreement with previously reported figures for other species.

Role of the Erythrocyte in Inhibition by Allantoic Fluid of Mumps Virus Hemagglutination.

A. L. FLORMAN. Proc. Soc. Exper. Biol. & Med., 75: 279, October, 1950.

It is shown that the inhibitor present in allantoic fluid for hemagglutination by and absorption of mumps virus is more active when human erythrocytes rather than when chicken red blood cells are used. It appears that the species of erythrocyte present influences the reaction between mumps virus and inhibitor in the direction of more or less combined (non-hemagglutinating) virus. A similar influence, though to a less striking degree, is also shown for the red blood cell in the influenza virus-inhibitor reaction.

Brain Tumors in Infancy and Childhood. S. W. GROSS. New York State J. Med., 50: 2267, October, 1950.

Brain tumors in infancy and childhood differ from those in later life in symptomatology, location and histologic type. In infancy, vomiting and rapid enlargement of the head should lead to a suspicion of brain tumor. In later childhood, awkwardness in use of the extremities, headaches, visual disturbances and convulsions may be additional symptoms. About two-thirds of all cerebral neoplasms in this age period are located in the cerebellum or fourth ventricle. The remainder are found in the brain stem, suprasellar region, optic chiasm, cerebral hemispheres and in the lateral and third ventricles. About 80 per cent of the tumors in infancy and childhood are gliomas. Meningiomas, neurinomas, pituitary adenomas and metastatic tumors occur very infrequently. Of the gliomas, medulloblastomas and astrocytomas comprise most of the neoplasms in this period of life. Craniopharyngiomas, sarcomas and teratomas also occur. In the differential diagnosis, the most important conditions to consider are stenosis of the aqueduct of Sylvius, subdural hematoma and chronic abscess.

The Therapeutic Management of Group Tension. W. C. HULSE. Am. J. Orthopsychiat., 20: 834, October, 1950.

This is a study of the therapeutic management of group tensions arising in two types of groups. The therapeutic group is one whose members have been selected by the therapist with psychotherapy as its sole purpose. The natural group is a group functioning realistically in day to day life, i.e. a family, or dormitory group, etc. The therapist does not try to eliminate anxiety and tension, but rather uses these dynamic factors for therapeutic purposes. Therapeutic sessions with family groups in the child guidance clinic at Mount

Sinai Hospital are used as examples for the demonstration of a new procedure in the treatment of anxiety and tension states.

Congenital Bilateral Aplasia of the Vas Deferens. A Factor in Male Sterility. LESTER NARINS. New York State J. of Med., 50: 2312, October, 1950.

Two cases of so-called "obstructive" sterility are described in which there was complete azoospermia with normal testicular biopsies. At operation both were found to have bilateral aplasia of the vas deferens. The embryology of this aberration is discussed. The author comments that the condition is far more prevalent than the paucity of similar case reports would lead us to believe.

Carcinoma of the Stomach Following Surgery for Chronic Duodenal Ulcer. D. ORRINGER. Surgery, 28: 680, October, 1950.

Carcinoma of the stomach is encountered infrequently as a complication of gastroenterostomy or gastric resection for chronic duodenal ulcer. A comprehensive review of the literature revealed only 27 such verified cases. The author collected five additional cases from the records of The Mount Sinai Hospital out of 1,160 cases diagnosed as carcinoma of the stomach, representing an incidence of 0.4 per cent. In all of the patients, melena or weight loss was noted. In only three was a history of pain elicited. Attention was directed to the fact that the recurrence of severe intractable epigastric pain, melena, hematemesis, anorexia and weight loss following surgery for duodenal ulcer may indicate the development of a carcinoma of the stomach rather than the more common complication, the benign marginal ulcer.

Fenestration by Cold Fracture Method: Preliminary Report of an Improved Technique. S. ROSEN. A.M.A. Arch. Otolaryng., 52: 618, October, 1950.

Improved hearing following the fenestration operation could be greater if it were not for bony closure of the fenestra. The author believes that heat and dust created by a motor driven burr during construction of the fenestra favor osteogenetic closure. He has devised a technique using tiny dental hand chisels which eliminate these factors of heat and bone dust. This technique is also available in instances in which the burr fails mechanically during the fenestration operation.

Suppression of the Phenomenon of Local Tissue Reactivity by ACTH, Cortisone and Sodium Salicylate. G. SHWARTZMAN. Proc. Soc. Exper. Biol. & Med., 75: 175, October, 1950.

ACTH, cortisone and sodium salicylate were capable of suppressing the phenomenon of local tissue reactivity. The dose of cortisone required for the inhibition was approximately 6 times greater than that of ACTH. Sodium salicylate completely inhibited the phenomenon in 17 out of 29 rabbits while in the remaining animals the reactions were strongly positive. Pantothenic acid, which had no effect upon the phenomenon by itself, enhanced significantly the suppressing effect of sodium salicylate.

Results of Midleg Amputations for Gangrene in Diabetics. S. SILBERT AND H. HAIMOVICI. J. A. M. A., 144: 454, October, 1950.

Two hundred and thirteen midleg amputations were performed for gangrene in 196 patients. One hundred and seventy-two amputations were done in diabetics, with a mortality of 9.3 per cent. Forty-one amputations were in nondiabetics, with a mortality of 9.7 per cent. Sixty-seven amputations were treated by primary closure, and 47 (70 per cent) healed by primary union. In 50 diabetic patients with gangrene who were treated with penicillin and midleg amputations with primary closure, there were three deaths, or a mortality of 6 per cent. In the entire group of 213 amputations there were 20 hospital deaths (9.4 per cent). Reamputation through the thigh was necessary in 10 cases (4.7 per cent). The advantages of mid-leg amputation over thigh amputation are lower mortality, preservation of better function and freedom from stump pain. With primary closure and

the use of antibiotics, healing by primary union may be expected in the majority of cases in three weeks and with a hospital mortality of 6 per cent.

The Sedimentation Differential Agglutination Test. D. STATS. Blood, 5: 950, October, 1950.

The sedimentation differential agglutination technique is a modification of the Ashby method by means of which the concentration of immunologically distinct erythrocytes in a mixture can be determined by observing their volume after agglutination and subsequent sedimentation. The method has been applied to the determination of the efficiency of replacement transfusions, the survival of red cells after blood transfusion, and has afforded a method for the determination of production of erythrocytes under certain conditions. The results indicate an almost complete inhibition of erythropoiesis and the frequent presence of excessively rapid hemolysis in blast leukemias.

Six Principles of Purchasing for the Equipment of New and Remodeled Areas. M. R. STEINBERG. Mod. Hosp., 75: 77, October, 1950.

For this article the author draws directly from the general policy evolved after much study for the equipment of Mount Sinai Hospital's three new buildings. There is given a technical description of extensive purchasing through a system which breaks down into area control for greater manageability. Forms of an area card, as well as item and alphabetical index cards, are shown. Also dealt with are matters such as overall purchasing to assure uniformity, the solicitation of expert advice in and out of the hospital, methods of assaying quantity and quality in relation to needs, seasonal purchasing and other marketing techniques calculated to assure low cost.

Cod Liver Oil Ointment Therapy in Proctologic Disorders. R. TURELL. New York State J. Med., 50: 2282, October, 1950.

The author described his favorable results with the use of cod liver oil ointment after the performance of anorectal operations as well as in the management of acute and subacute perianal, nonspecific, dermatitides with or without pruritus.

Adenomas of the Colon and Rectum. R. TURELL AND R. S. WILKINSON. Surgery, 28: 651, October, 1950.

In this paper the histogenesis, diagnosis and treatment of adenomas of the colon and rectum are presented.

Blood Exchange in Replacement Transfusions. 1. Theoretic Considerations. L. R. WASSERMAN AND L. SHARNEY. Blood, 5: 925, October, 1950.

Exchange transfusions of blood have proved to be of value in severe cases of erythroblastosis fetalis, in patients with anuria, in certain toxemias, and in acute leukemia. The procedure may be performed by the discrete technique in which equal volumes of blood are administered and withdrawn alternately, or as a continuous exchange in which blood is injected and withdrawn simultaneously. Mathematical formulae are derived for the theoretic effectiveness of both types of exchange. Graphs are constructed from the equations so that by employing the values for the initial blood volume of the subject and the volumes and hematocrits of the blood transfused and withdrawn, one may calculate the degree of red cell exchange. Conversely, one may determine the amount of blood necessary to exchange in order to achieve a particular degree of replacement.

Blood Exchange in Replacement Transfusions. 11. Studies with Erythrocytes Tagged with Radioactive Phosphorus. L. R. WASSERMAN, I. A. RASHKOFF, L. SHARNEY, TSE-FEI YOH, AND D. LEAVITT. Blood, 5: 938, October, 1950.

The applicability of the mathematical expressions derived in the previous paper to actual experimental results is presented. Methods for the measurement of blood volume and for the identification and quantitative determination of exchanged red cells by tagging

the erythrocytes with radioactive phosphorus are described. Replacement transfusions were performed in ten subjects with leukemia and other neoplastic diseases. Values for the theoretically calculated and actually observed degree of blood exchange are noted to be in excellent agreement. It is concluded, that since the experimental results confirm the theoretic formulations, these curves and formulae may be utilized whenever exchange transfusions are to be performed.

Adrenal Cortex in Liver Disease. J. J. WEBSTER. *Ann. Int. Med.*, 53: 854, October, 1950.

A first group of 9 patients (cirrhosis, 4; homologous serum jaundice, 1; chronic active infectious hepatitis, 1; chronic hepatitis with "pseudo-colic," 1; arsenical hepatitis, 2) was treated with aqueous and oil extracts of adrenal cortex. All were rapidly going downhill despite usual therapy. All recovered promptly and laboratory tests reverted to normal. Reexamination after a year revealed no evidence of liver dysfunction. There was evidently: (1) psychic stimulation; (2) alteration of the carbohydrate-protein metabolism with glyconeogenesis from protein, deposition of liver glycogen, possible formation in the liver of α_2 -globulin (hypertensinogen), changes in blood and sugar levels; and (3) sodium and fluid retention with potassium excretion and changes in body hair and pigment. Of 3 patients with hyperglycemia, one had a Cushing-like syndrome with possible permanent diabetes; two patients had hypertension, two had unexplained precordial distress, and all had latent edema. There was remission of complicating ulcerative colitis in one case. The further use of the drug in colitis and the sprue syndrome is being investigated. Care must be used in administration of adrenal cortex extracts. Literature is reviewed and theories of action are discussed. Unlike the reported experience with ACTH and cortisone, extract of adrenal cortex may be discontinued when recovery is noted. It is believed that this is evidence of a true physiologic effect, possibly in balancing an adaptive homeostatic regulating mechanism or in the actual regeneration and repair of damaged liver cells.

Aerosols II. The Role of Particle Size in Inhalation Therapy by Atomization and by Pencillin Dusts. H. A. ABRAMSON. *Dis. of Chest*, 18: 435, November, 1950.

The particle size distribution of the droplets of atomized liquids and 3 particulate dusts have been measured. The particle size distribution of a commercially available atomizer, especially designed to produce small particles revealed that approximately 6 per cent by weight of the droplets produced by this atomizer may reach the aveolar ducts. Three samples of commercially available penicillin dusts designed for inhalation therapy show important differences in the particle size distribution. One of these dusts has particles so large that it is practically useless for therapy of the lungs. Two others have particle size distributions by which approximately 40-80 per cent of the particle weight may reach the aveolar ducts. The difficulties of using dusts with tropical storage and maintenance of suitable particle size distribution is pointed out. It is emphasized that if penicillin dust therapy is to be suitable at all, the particle size distribution must be so designed that penetration into the nose, oropharynx and larynx of a reasonable fraction should be possible.

Pruritus Vulvae due to Aureomycin. H. T. BEHRMAN. *J. A. M. A.*, 144: 995, November, 1950.

Within the past few months, the author observed several cases of pruritus vulvae following aureomycin therapy. This observation has also been made by several dermatologists and internists who have had frequent occasion to use aureomycin in the treatment of various diseases. In the usual case, the patient complains of itching of the vulva and vaginal introitus within several days to one week after the ingestion of the drug. Examination of the genital area may reveal no signs other than a few superficial excoriations and slight erythema. In 2 instances, both inguinal folds showed numerous minute vesicopustules with surrounding erythema. Scrapings and cultures of these lesions and the vaginal introitus showed *Monilia* (*Candida*) *albicans* in one case. The associated pruritus gradually subsides spontaneously. It may be relieved by bland lotions and antihistaminics given

internally. In the patient in whom *Monilia* was found, the eruption responded rapidly to sodium propionate (5 per cent) douches and local application of a 15 per cent sodium propionate ointment. One possible explanation of this cutaneous phenomenon may be presumed due to the effects of aureomycin on normal vaginal flora. The drug probably destroys local organisms with the exception of members of the yeast family. Once the restraining presence of these other organisms is removed, the *Monilia* proliferate actively and give rise to a typical monilial vulvo-vaginitis. Several patients have also complained of pruritus ani during a course of aureomycin therapy. Pruritus vulvae is one of the complications of aureomycin therapy. This report advances a possible explanation for this condition. The local process responds rapidly to external fatty acid therapy. Anal pruritus may also be encountered as a side reaction to this drug.

An Experimental Study of the Cardiovascular Effects of Diodrast. A. J. GORDON, S. A. BRAHMS, S. MEGIBOW, AND M. L. SUSSMAN. *Am. J. Roentgenol.*, 64: 819, November, 1950.

When given intravenously in 70 per cent solution, in large amounts and as quickly as possible, diodrast has the following effects on the intact dog anesthetized with nembutal: A rise followed by a fall of arterial blood pressure; a rise in pulse pressure associated with marked changes in the contour of the femoral pulse; a rise in venous pressure and a fall in the pulse rate; and changes in the electrocardiogram. This typical "diodrast reaction" can be modified by changes in the speed of the injection but is not completely eliminated even when the injection is given very slowly. The most significant of the diodrast actions is vasodilatation. Stimulation followed by depression of the cardiac muscle occurs. Efforts to prevent the vasodilatation by abdominal compression or the use of various drugs, failed. No evidence of allergic sensitization occurred in animals receiving two injections of diodrast several weeks apart.

Distribution of Absorbed Energy around a Point Source of Beta Radiation. R. LOEVINGER. *Science*, 112: 530, November, 1950.

The rational use of radioactive materials in biology and medicine requires knowledge of the amount and distribution of the dose delivered to tissue by the radiations. For isotopes emitting beta particles, information has not previously been available concerning the distribution of dose around small sources. If the dose distribution is known for a point source, it can be computed for any known distribution in tissue. A method is described for calculating this point source distribution from measurements made on a thin, flat source. The results of such measurements on radioactive phosphorus (P^{32}) are given in the form of simple mathematical expressions, from which the dose to tissue can be computed directly for any known distribution of the isotope in tissue.

Hystero-graphy and Hysterosalpingography. An Evaluation of 2,500 Cases. M. A. GOLDBERGER, R. MARSHAK, AND A. DAVIDS. *New York State J. Med.*, 50: 2607, November, 1950.

The authors reviewed 2,500 cases in which hystero-graphy or hysterosalpingography was done, in an effort to evaluate these procedures and determine their safety. The indications for contrast visualization of the uterus and tubes are menometrorrhagia, dysmenorrhea, sterility, fibroid uterus, postmenopausal bleeding and congenital anomalies. Contraindications are acute and subacute pelvic inflammatory disease, intra-uterine pregnancy, chronic cervicitis with purulent discharge, vaginitis, active uterine bleeding, and serious constitutional disease. The authors use the standard fractionated method of study. Water-soluble media have been found very satisfactory despite the fact that they do not permit a 24-hour film. The more viscous materials are excellent for hystero-graphy but, when employed to visualize the tubes, they may in rare instances result in fat granulomas and emboli. The following conditions have been demonstrated: endocervical and endometrial polyps, intramural and submucous uterine fibroids, hyperplastic endometrium, endocervicitis, retained products of conception, pregnancy, ovarian tumors, carcinoma, tuberculous endometritis, congenital anomalies, and ante-flexion and retroflexion of the uterus. With

hysterosalpingography it has been possible to demonstrate patency of the tubes, spasm, hydrosalpinx with and without closure of the tubes, site of tubal occlusion, displacement of the tubes, tuberculous salpingitis, and ectopic gestation. Complications are not serious. They include pain, peritoneal irritation, endometritis, emboli, allergic phenomena, and, more rarely, hemorrhage, perforation of the uterus, acute exacerbation of chronic pelvic inflammatory disease, shock, entrance of dye into the uterine vascular structure, and its introduction into a pregnant uterus. The serious complications are so rare that they should not be considered a contraindication to the procedure.

Value of Hystero-graphy in the Diagnosis of Large Submucous Uterine Fibroids. R. H. MARSHAK, M. A. GOLDBERGER, AND W. A. EPSTEIN. *Radiology*, 55: 725, November, 1950.

Large submucous fibroids when they occupy the entire uterine cavity form a false smooth wall, and are difficult to detect by curettage. Three case reports are presented in which curettage done because of abnormal bleeding showed no evidence of any tumor within the uterine cavity. Subsequent hystero-graphs, however, revealed the uterine cavity to be enlarged, globular in outline with filling defects typical of a submucous fibroid. Rayopaque and skioidan acacia were the contrast media employed. No attempt was made to visualize the tubes in these cases and no ill effects were observed from the use of the drugs in this series.

Measurement and Significance of Urinary Appearance Time in the Dog. P. A. MORALES, C. H. CROWDER, A. P. FISHMAN, M. H. MAWXELL, AND D. M. GOMEZ. *Am. J. Physiol.*, 163: 454, November, 1950.

The urinary appearance time signifies the time interval from the moment of intravenous injection of a test substance to its first detectable appearance in the urinary bladder. It includes the circulation time from the site of injection to the glomerular or tubular vessels, and the time for the substance to travel from the site of excretion down the tubules, through the pelvis and ureters, and into the bladder. In dogs with exteriorized bladder, despite wide range in urine flow, the appearance time remained practically constant. Indigo carmine, phenolsulphonphthalein, PAH, inulin, and sodium ferrocyanide were used as test substances. These data indicate a passive dilatation of the renal tubules with increase in urine volume. This measurement is significant with regard to clearance techniques in renal physiology where a correction is made for "delay time" in order to relate a given urine sample to blood from which the urine is formed.

The Role of the Antihistaminic Drugs in Producing Cross-Sensitization Dermatitis. S. M. PECK. *New York State J. Med.*, 50: 2690, November, 1950.

Recurrent and persistent dermatoses found in and out of industry are at times due to cross-sensitization to chemicals whose possession of a common immuno-chemical grouping is unsuspected. Among such chemicals are the antihistaminics which are being used freely in industrial plants for the control of the common cold. A sensitivity developed to one antihistaminic may lead to sensitivity not only to other antihistaminics with related immuno-chemical groups, but to apparently unrelated chemicals.

Teaching Fenestration Surgery. (Editorial). S. ROSEN. *Am. J. Surg.*, 80: 491, November, 1950.

In the past 10 years or so, about 80 per cent of the otologists who have made every effort to learn the fenestration operation according to the prescribed course are not doing the surgery. They found that they were not expert enough in the technique after having operated 15 to 20 cadavers. The author found that the reason for so many non-performers was the inadequate amount of cadaver surgery. The formal course in fenestration surgery should explicitly denote that, as a rule, a student who finishes the course is not yet ready for the operating room. The author recommends, therefore, 100 cadaver operations before performing surgery on patients. The principle of practice makes perfect is simple and some

will feel offended that such an obvious principle should be so stressed. Yet objective analysis would indicate that no matter how much this simple principle is approved verbally, in most cases it is not fully applied in practice.

An Evaluation of Aureomycin Therapy in Primary Atypical Pneumonia. E. B. SCHOENBACH, A. SWEED, B. TEPPER, AND M. S. BRYER. *New England J. Med.*, 234: 799, November, 1950.

The disease, primary atypical pneumonia, had been found unaffected by chemotherapy prior to the use of aureomycin. In 1948 and again in 1949 a series of patients were reported in whom a beneficial effect with aureomycin was apparent. A series of 33 consecutive patients with primary atypical pneumonia treated with aureomycin was compared with 22 patients who had been treated with penicillin or sulfonamides. It was found that although the day when therapy was begun in both groups was comparable the duration of fever for the penicillin group was $6.4 \text{ days} \pm 0.85 \text{ day}$ and for the aureomycin group $1.8 \text{ days} \pm 0.23 \text{ day}$. Thus the total duration of illness was $13 \text{ days} \pm 1$ for the penicillin group and $7.8 \text{ days} \pm 1$ for the aureomycin group. This data further established the efficacy of aureomycin in primary atypical pneumonia.

Blood Levels of I-131 After Tracer Doses in the Diagnosis of Hyperthyroidism. S. SILVER AND M. H. FIEBER. *Proc. Soc. Exper. Biol. & Med.*, 75: 570, November, 1950.

A new test for hyperthyroidism is presented based upon the determination of the protein-bound radioactivity of the blood serum after tracer doses of I-131. It is shown that a single determination performed on one cubic centimeter of serum drawn at 72 hours after the administration of 100 microcuries of I-131 by mouth suffices for the diagnosis of hyperthyroidism and offers a sharp differential between the hyperthyroid and normal patients.

Neo-Fatty Acids. H. SOBOTKA AND F. E. STYNLER. *J. A. C. S.*, 72: 5139, November, 1950.

The syntheses, properties and infrared absorption spectra of neo-palmitic and neo-stearic acid and of the neo-isomers of arachidic, behenic and lignoceric acids are described as well as the preparation of neo-octyl chloride. The neo-isomers are characterized by triple branching at the end of the aliphatic chain leading to an accumulation of three methyl groups.

Clinical Electroencephalography. MORTIMER OSTOW. *Acta med. Orientalia*, 9: 267, November-December, 1950.

This is a brief summary of the present day status of electroencephalography from the point of view of the clinical neurologist. The normal and the abnormal electroencephalographic patterns are described. The relationship between pathologic processes in the brain and distortions of the electroencephalographic pattern is presented. From this data the theory of diagnostic electroencephalography is derived.

The Role of Denial in Acute Postoperative Affective Reactions Following Removal of Body Parts. V. H. ROSEN. *Psychosomatic Med.*, 12: 356, November-December, 1950.

Four patients from the Surgical Service who developed severe affective reactions (1 manic and 3 depressive) following the removal or alteration of major portions of the body were studied psychiatrically. The following conclusions were reached: 1. The seemingly appropriate "mourning" response to the loss of an important body part or function should be regarded as pathological when it forces the patient into a regressive reaction in which he ceases to make spontaneous and active attempts at readjustment. 2. The reaction is best understood in terms of the development of the ego's capacity for active mastery by the formation of the defense of "normal" denial as described by Anna Freud. The most severe reactions occur in those individuals who show an exaggerated quality of independence achieved through denial of danger. 3. The modifiable factors lie in the ability to predict

preoperatively which personalities will require special psychological preparation for operation by describing to them what the new postoperative body image will be like in terms that carry emotional as well as intellectual understanding.

Mental Changes in Intracranial Tumors and Related Problems. B. SCHLESINGER. *Confinia. Neurol.*, 10: 225, November-December, 1950.

The psychopathologic manifestations encountered in 591 cases of verified intracranial expanding lesions were tabulated. Mental changes, present in 51 per cent included: (a) disturbances in consciousness, (b) in affect, behaviour and personality and, (c) in intellect. In 286 cases of unilateral lesion of the cerebral hemispheres, the incidence of mental changes was highest among patients with either frontal or temporal lobe tumor. In the group of frontal lobe tumors, symptoms were present in 80 per cent of 36 basifrontal lesions, and in 65 per cent of 93 tumors occupying the convexity and central white matter of the frontal lobe. In the temporal group, depending on whether the right (24 cases) or the left (34 cases) temporal lobe was involved, the incidence of mental changes reached, respectively 71 per cent and 89 per cent. Frontal lobe tumors of either right or left side were equally effective in producing mental changes. Rolandic lesions showed the lowest incidence of mental changes, namely 38 per cent of 45 cases. The curve indicating the total number of psychic changes showed in general a steady fall as the lesion approached the rolandic fissure, using the temporo-occipito-frontal axis of the hemisphere as line of reference. In the group of frontal lobe tumors, the incidence of emotional changes was apt to be higher than in the other groups, among which intellectual deterioration was the most frequent abnormality. Disturbances in consciousness were most frequent among patients with frontal tumors (37 per cent), least frequent among patients with rolandic neoplasms (4 per cent). Ninety-two per cent of 50 bilateral frontal lobe lesions exhibited mental changes, chiefly emotional disturbances, (78 per cent), while among a group of 19 tumors involving the splenium of the corpus callosum the total incidence of mental abnormality was 89 per cent, and that of disturbance in affect only 26 per cent. The pattern of mental disturbance with thalamus, hypothalamus and midbrain (37 cases) resembled that in frontal lobe tumors. Mental changes among patients with infratentorial tumors (126 cases) were present in only 16 per cent. The validity of the various data for the entire group of 591 cases appears to be enhanced by the fact that mental changes produced by newgrowths as could be ascertained by an extensive perusal of the literature, were similar to those encountered in patients with vascular and degenerative lesions involving comparable parts of the brain, by injuries and also by experimental lesions in higher primates. Mental changes in frontal lobe tumors are, furthermore, similar to those following psychosurgical procedures, particularly bilateral lobotomies carried out for the relief of pain in mentally normal individuals. In evaluating the above data, the high incidence of mental changes in both frontal and temporal lobe tumors, of emotional disturbances in frontal and mesencephalic lesions, and of intellectual disturbances proper in disease of the posterior associational areas, particularly the temporal lobes, appeared to be of significance. Curves, corrected for standard error, illustrated the behaviour of the various sets of values computed (a) for the total and (b) for the individual disturbance patterns of the three subgroups of psychiatric manifestations plotted against the regional varieties of neoplasms. The general trend in all sets of data which together formed a consistent pattern was too conspicuous to be coincidental. This trend was not significantly modified either by the height of the intracranial pressure, or the distant effects exerted by the lesions or their histologic character. Neither was there any demonstrable relationship between the disabling effects of headaches and of convulsions on the one hand, and of mental changes on the other. The personality type of the patient of course did not account for the shape of the curves. On the basis of the available evidence it appeared legitimate to assume that presence and type of mental changes depend primarily on the side of the lesion. Since the behaviour of the various numerical values reflects disturbance patterns as determined for the various groups rather than individual cases (where the general pattern is apt to be obscured by chance factors), the localizing value of mental

changes is of but limited practical significance. From a theoretical viewpoint their classification into those disturbances in affect and in consciousness and in intellect appears to be vindicated by general biologic considerations. Apparently, the various agencies concerned with the integration of mental performances contribute different quotas of action to the total process. It is suggested that the autonomic system, extending from the brainstem to the frontal lobes, determines awareness, volume control and type of responsiveness, that is to say, affective behaviour while cognitive functions appear to be vested in the posterior part of the cortex. The autonomic factor which, at the highest level is concentrated chiefly in the frontal lobes, exerts a homeostatic influence over both the emotional and the intellectual sphere and determines, at the same time, the level of general psychomotor activity, of attention and concentration. The intrinsic neural mechanism subserving precision and creativity of thought on the other hand, would seem to depend on the posterior associational fields which are but an elaboration of the primary receptive areas. Psychic phenomena, then, may be thought of as occurring within the general framework of the organism, from a biophysical point of view a stratified input-output system in which energy is transformed in such a way as to maintain a steady state, and in which the equilibrium of vital functions makes higher activities possible. However, the higher functions do not essentially differ from the lower. In the neural sphere, the input-output character of the organism is expressed by the sensory-motor organization of the nervous system, and its stratification by the fact that, at the top level, the mode of action of the lower strata is raised to higher powers. At the highest level, the elementary sensory agencies have become elaborated to the mechanism subserving thought; the motor sphere to the highly differentiated cortical instrumentalities subserving skilled movement, and the autonomic sphere to the agencies mediating affective behaviour. Therefore, in studying the site-relatedness of mental functions and their disturbances in organic lesions of the brain, an appreciation of the role of the lower strata appears to be essential for that of the higher.

A Method of Automatic Controlled Respiration for Anesthesia in the Dog. M. H. ACELMAN, S. J. MEGIBOW, AND L. BLUM. *Surgery*, 28: 1040, December, 1950.

A simple, economic and dependable method of maintaining automatic controlled respiration in the anesthetized dog is presented. The technique utilizes the pneumatic balance resuscitator, an automatic respirator which converts continuous positive pressure into intermittent positive pressure. The respirator is attached to an endotracheal tube with an inflatable cuff since an almost airtight system is needed for proper functioning of the apparatus. The basic anesthetic agent used is intravenous veterinary Nembutal. In a series of prolonged experiments, some involving exclusion of the heart with major alterations in circulation, the method has proved of great value.

Healing of Fractures, Editorial. E. M. BICK. *Am. J. Surg.*, 80: 543, December, 1950.

A fracture is classically defined as a traumatic dissolution of continuity of bone. The actual incident of trauma is in itself the effective stimulus to a chain of physiologic reactions which in predictable sequence constitutes the process of reparative osteogenesis. This process is entirely a local one. Any systemic reaction such as vasomotor, metabolic or endocrine which occurs in a patient whose bone is broken is incidental and not related to the healing of that bone. Two hundred years of intensive investigation have failed to discover any consistent effect exerted by normal systemic processes upon the local phenomena of reparative osteogenesis. The present difficulty in all fracture treatment is the inability to determine the effective healing point post-fracture. This phenomenon is defined as that point during the process of healing at which callus has been formed in sufficient strength to enable the bone to withstand the stresses and strains to which it is normally accustomed in its sound state. It is reached long before x-ray films show evidence of complete remodelling. Several types of evidence suggest that the healing point has been attained, but only an appreciation of the histologic process of reparative osteogenesis can furnish the knowledge upon which adequate judgement can be based.

Partial Gastric Resection For Peptic Ulcer Of The Esophagus. A. CORNELL AND A. WINKELSTEIN. *Gastroenterology*, 16: 720, December, 1950.

The treatment of peptic ulcer of the esophagus has heretofore been very difficult. Perforation of such an ulcer is usually fatal and occurs in 14 per cent of cases. The present case is of interest because an intractable esophageal ulcer was cured by means of partial gastric resection. Intraesophageal drip therapy with alumina gel mixtures caused definite healing of the esophageal ulcer with relief of symptoms for a period of time. The presence of duodenal ulcer associated with esophageal ulcer is an added indication for partial gastric resection. From a prophylactic, therapeutic, and physiologic viewpoint, partial gastric resection seems to be the best means of curing a peptic ulcer of the esophagus and its equivalent (peptic esophagitis) and for preventing complications (esophageal stricture, mediastinal perforation, hemorrhage, and malignant transformation).

Deoxycortone and Ascorbic Acid in Rheumatoid Arthritis. S. DAVISON. *Lancet*, 2: 770, December, 1950.

Twenty patients with Rheumatoid Arthritis received daily injections of 5 mg. of deoxycorticosterone intramuscularly followed by 1 gram of ascorbic acid intravenously. The length of treatment varied from 1 to 8 days. In 1 case the blood pressure rose during therapy. In another instance (arthritis, scleroderma, hypertension and luetic aortitis), acute pulmonary edema may have been precipitated by the medication. Only 4 patients reported subjective improvement. The overall results were very unsatisfactory and do not confirm the report of Lewin and Wassen.

A New Nasal Splint. I. B. GOLDMAN. *Arch. of Otolaryng.*, 52: 962, December, 1950.

The new nasal splint here described differs from other varieties in the following respects: 1. There is a left and right thread. When the center screw is turned pressure is therefore applied equally to both nasal bones. 2. The screw is turned from the top preventing a shift in position while pressure is applied. 3. The centrally placed overhead band gives a perfect fit and prevents the splint from slipping. 4. The lateral bands are supplied with hooks which fit into the side bars. These bands are removable and washable. Some of the precautions necessary in the use of nasal clamps are as follows. The osteotomy must be complete in order to place the splint correctly. Application on a greenstick fracture usually results disastrously. The skin of the dorsum must be elevated in a proper plane; if it is elevated too near the surface necrosis of the skin may occur following placement.

The Diagnostic Significance of Urinary Pepsinogen Excretion in Diseases of the Upper Gastrointestinal Tract. H. D. JANOWITZ, M. H. LEVY, AND F. HOLLANDER. *Am. J. Med. Sciences* 220: 679, December, 1950.

The hourly rate of urinary pepsinogen excretion was determined on 99 subjects in the fasting condition, using a 3-hour specimen in each case. Thirty-five subjects with active duodenal or stomal ulceration excreted, on the average, 4 times as much uropepsin as did the 44 control subjects. A group of 12 patients with gastric neoplasms and gastric ulcers excreted normal amounts of uropepsin. Seven patients with pernicious anemia, and 1 with a total gastrectomy excreted no uropepsin whatever. The determination of urinary pepsinogen excretion appears to have considerable value as an addition to the conventional diagnostic approach to disorders of the upper gastrointestinal tract. This is especially true in the bleeding patient and in the patient with a neutralization anacidity following a gastrointestinal anastomosis.

A Rapid Method for Determination of Blood Urea Nitrogen. H. LEAR. *J. Urol.*, 64: 818, December, 1950.

In this article, a rapid method for the determination of blood urea nitrogen is described. With the technique presented a blood urea nitrogen can be performed in five minutes, using

a reagent, and a simple ureometer. It is accurate within 4 mg. %, and should prove useful for routine office practice or emergency hospital determinations.

Penicillin Prophylaxis of Postoperative Bacteremia and Bacterial Endocarditis. P. A. LICHTMAN AND A. M. MASTER. *M. Ann. Dist. Columbia*, 19: 663, December, 1950.

In 406 consecutive autopsies in patients 50 years old or more, 342 (84.2 per cent) disclosed evidence of heart disease. Rheumatic lesions were present in 176 (51.4%), arteriosclerotic in 133 (39.0%), and a miscellaneous group of lesions in 33 (9.6%). It has been indicated that any type of heart disease, particularly valvular, which produces damage of endocardial tissues may predispose to subacute or acute bacterial endocarditis during postoperative bacteremia. Since valvular lesions are very common in persons over 50, although often not obvious clinically, penicillin prophylaxis prior to operation and diagnostic or manipulative procedures may be instituted to obviate the development of bacteremia and bacterial endocarditis. The dosage and method are described.

Clinical Isodose Curves. R. LOEVINGER, B. S. WOLF, AND W. MINOWITZ. *Am. J. Roentgenol.*, 64: 999, December, 1950.

The instrumentation, techniques, and results of certain water phantom measurements of conventional therapeutic X-rays are described. It is shown that some generalizations may be made concerning depth dose measurements in phantoms of limited size. The depth dose curves, both on and off the beam axis, are quite generally exponential (that is, straight lines on semi-logarithmic plots) modified by proximal and distal transition regions. As a result, the general problem of clinical isodose curves in tissue of limited size appears to be less complex than was once anticipated. Application of the method to treatment of cancer of the larynx with two opposing fields is given.

Post-Bulbar Duodenal Obstruction in Carcinoma of the Pancreas. R. H. MARSHAK, D. A. DREILING, AND A. I. FRIEDMAN. *Gastroenterology*, 16: 680, December, 1950.

Pyloric or duodenal obstruction is not usually the presenting feature in tumors of the pancreas. Yet, 4 female patients were asymptomatic until carcinoma of the pancreas produced marked post-bulbar obstruction of the duodenum. Roentgenologically, a constriction of the second portion of the duodenum producing obstruction is most likely due to peptic ulcer, metastatic nodes, retroperitoneal sarcoma, annular pancreas, primary carcinoma of duodenum or ampulla of Vater and carcinoma of the pancreas. A brief differential diagnosis would consider that primary carcinoma of the duodenum or ampulla of Vater usually presents little narrowing of the duodenum; an annular pancreas is more commonly symptomatic early in life; nodes or retroperitoneal tumors usually produce a widening of the duodenal loop while post-bulbar ulcer often presents a history of ulcer symptoms, and complete obstruction is uncommon.

Megacolon. A Complication of Ulcerative Colitis. R. H. MARSHAK, L. J. LESTER, AND A. I. FRIEDMAN. *Gastroenterology*, 16: 768, December, 1950.

The development of megacolon in ulcerative colitis is an extremely rare complication. This may be due to the fact that in megacolon, the nerve plexuses of Meissner and Auerbach are atrophied while in ulcerative colitis they are hypertrophied. Neurohistopathology in the sigmoid may cause acquired megacolon just as lesions in the rectum are responsible for some cases of congenital megacolon. A 46 year old male with a 4 year history of severe ulcerative colitis developed a perforation of the colon near the splenic flexure for which a cecostomy was performed by Dr. R. Colp. Three years later, a barium enema revealed a hugely distended large bowel beginning at the sigmoid and involving the remainder of the proximal colon like that usually seen in megacolon.

Pheochromocytoma with Calcification Simulating Cholelithiasis. Report of a Case. M. MOSER, G. SHEEHAN, AND HAROLD SCHWINGER. *Radiology*, 55: 855, December, 1950.

A case of pheochromocytoma with circular calcification occurring in a 44 year old Negro male is reported. The patient was admitted to the hospital with a three month history of right upper quadrant pain, nausea and vomiting, and profuse sweating. Intermittent hypertension, a persistent "insulin resistant" type of diabetes and evidence of hypermetabolism were noted. X-ray examination revealed a circular calcific shadow, 2 cm. in diameter, in the right upper quadrant above the gall bladder. The shadow was fixed in position posteriorly and was 3 cm. below the diaphragm. Intravenous pyelograms showed a rotation of the right calyseal system with the calcific density above the right kidney. An intravenous test with 100 mg. of tetraethyl ammonium chloride (Etamon) resulted in a rise in blood pressure within 3 minutes from 230/130 to 250/150; a positive test for an adrenaline secreting tumor. The patient refused surgery and expired three months later following a cerebral hemorrhage. Necropsy confirmed the diagnosis of a pheochromocytoma of the right adrenal gland. The tumor weighed 300 gm. and contained a ring shaped calcific area 1.5 cm. in diameter within its upper pole.

Tympanomeatal Membrane in the Fenestration Operation. Its Relation to Bony Closure of the Fenestra. S. ROSEN. Arch. Otolaryng., 52: 930, December, 1950.

One of the avoidable causes of closure of the fenestra in the operation for otosclerotic deafness is fine spicules of bone adherent to the skin flap which covers the fenestra. After removing 150 such skin flaps from fresh cadavers and removing all adherent bone spicules under 10 power magnification, these skin flaps were X-rayed. The X-ray revealed bone chips still present in over half the cases. A modification of Lempert's technique therefore was described in which that portion of the tympanomeatal flap which always covers the fenestra will remain completely free from any adherent fractured pieces of bone, thereby eliminating an avoidable cause for failure of the fenestration operation.

Right-Sided Aortic Arch. P. SAMET AND D. J. STONE. Am. Heart J., 40: 951, December, 1950.

This paper deals with the problem of aortic arch anomalies. There are two types of right aortic arches without inversion of the heart itself. The first, or anterior, type is that in which the aortic arch is anterior to the trachea, with the descending aorta on the right side. The second, or posterior, type is that in which the aortic arch is retroesophageal, with the descending aorta coursing to the right of its normal position but still descending on the left side. It is felt by some investigators that the first type is more common in association with other cardiac abnormalities while the posterior type is the rule in otherwise normal hearts. A case report of the incidental finding of the first type of right aortic arch (with the heart otherwise normal) in a middle-aged male is given. Tomograms, esophograms and angiocardigrams confirmed the diagnosis.

Enhancing Effect of Cortisone upon Poliomyelitis Infection (Strain MEFl) in Hamsters and Mice. G. SHWARTZMAN. Proc. Soc. Exper. Biol. & Med., 75: 835, December, 1950.

ACTH and cortisone in combination or cortisone alone produce a marked acceleration of poliomyelitis infection (strain MEFl) in mice and an extraordinary enhancement of susceptibility to this infection in hamsters giving rise to a violent and uniformly fatal disease. ACTH alone fails to produce this effect possibly due to elaboration of an unknown factor capable of reversing the enhancing effect of cortisone. The experiments seem to indicate the existence of a significant relation between adrenocortical function and susceptibility of mice and hamsters to experimental poliomyelitis.

Shortening of Bleeding Time by a Water-Soluble Adrenochrome Derivative. H. SOBOTKA AND N. ADELMAN. Proc. Soc. Exper. Biol. & Med., 75: 789, December, 1950.

Trimethylammoniumacetylhydrazine hydrochloride of L-adrenochrome (T.A.L.) is a potent hemostatic agent. It shares this property with the parent substance adrenochrome, but surpasses it by stability and solubility in aqueous solution. It may be injected intramuscularly in children in amounts of 10 mg. without producing local reactions. A single

injection of this amount shortens the bleeding time, as measured by Ivy's method, by an average of 38% in 32 subjects; except for 7 non-responsive cases with short pre-injection bleeding time, the mean bleeding time in the remaining 25 cases is cut in half. Only individuals with a short bleeding time fail to respond. Control tests show that the concomitant surgical intervention has no influence on bleeding time.

Films of Hydrocarbon-Stearic Acid Mixtures. H. SOBOTKA AND S. ROSENBERG. *J. Colloid Science*, 5: 581, December, 1950.

The formation of monomolecular layers on a barium buffer hypophase and of built-up Y-films is described for various mixtures of stearic acid with n-octadecane, n-octacosane, and n-hexatriacontane. The thickness of the resulting mixed films is interpreted with reference to their structure. The existence of a limiting proportion of 1 molecule of hydrocarbon to 2 molecules of stearic acid is explained by the crystal structure of the films. The relationship between three-dimensional and two-dimensional molecule compounds containing aliphatic acids is discussed. The experiments reported in this paper illustrate the extension of monomolecular layer techniques to substances which do not spread by themselves.

Films of Omega-Branched Fatty Acids. H. SOBOTKA, S. ROSENBERG, AND A. BIRNBAUM. *J. Colloid Science*, 5: 567, December, 1950.

The investigation deals with the effect of terminal branching upon the behavior of long-chain aliphatic acids. Monomolecular layers of these compounds, spread on buffer solutions, are characterized by determination of the force/area relationship. On the basis of their minimum molecular area in condensed films, the tilt of the molecule against the surface was computed and various possibilities for the conformation of the terminal groups were evaluated. The capability of building up polylayer films on a solid surface and the character of such films reflects the shape of the molecule and its deviations from the prismatic form. A number of surface phenomena such as contact angles, surface reflection, and skeletonization by dissolving the free fatty acids in the film are treated. Although films of branched fatty acids resemble those of normal fatty acids in several points, a striking difference is revealed by their enormous surface volatility. Molecular sublimation of branched fatty acids across blankets of stearic acid, several hundred Angstrom units thick, is an important manifestation of the dynamic state prevailing in crystalline polymolecular films.

Further Experiences in Treatment of Septic Meningitis with Bacitracin. P. TENG. *Arch. Neurol. & Psychiat.*, 64: 861, December, 1950.

Thirteen patients with purulent meningitis have been treated with bacitracin. The following organisms were found: staphylococcus in 6, streptococcus in 2, pneumococcus in 1, mixed in 2 and an unidentified Gram-positive coccus in 2. In this series 8 patients were treated with bacitracin, after penicillin and/or other antibiotics and sulfonamides had failed, 6 of these survived and may be called salvaged cases. Five patients were treated primarily with bacitracin by intracranial and subarachnoid therapy supplemented with systemic penicillin and bacitracin. Nine patients recovered and 4 died. One died from an irremovable tumor in the pineal region which caused complete block of the ventricular system and meningitis, 1 from a middle cerebral artery thrombosis with extensive cerebral infarction and infection of the brain tissues, 1 from multiple brain abscesses and a long-standing extensive purulent encephalitis, and 1 from an undisclosed brain abscess, meningitis, bronchopneumonia and cardiac failure. Among the survived patients, the youngest was 6 weeks and the oldest 76 years of age.

An Evaluation of Present Day Surgical Procedures in Diseases of the Lower Bowel. R. TURELL AND R. S. WILKINSON. *New York Med.*, 6: 16, December, 1950.

In this paper the newer aspects of proctologic disorders were presented primarily for the benefit of the general practitioner and non-proctologic specialists.

The Syndrome of Anosognosia. E. A. WEINSTEIN AND R. L. KAHN. A.M.A. Arch. Neurol. & Psychiat., 64: 772, December, 1950.

Anosognosia (the denial of illness or defects) was observed in 22 cases of brain tumor. The tumors were situated in various parts of the brain including the frontal, temporal and parietal lobes, the diencephalon and the posterior fossa. In 17 cases there was increased intracranial pressure and/or subarachnoid bleeding. In the remaining 5 cases the lesion extended across the midline and involved the regions of the third and lateral ventricles. In 16 of the 17 cases with electroencephalographic records, bilaterally diffuse abnormalities were noted. In all instances more than one aspect of illness was denied. Anosognosia never occurred as an isolated phenomenon but was manifested as part of a generalized disturbance of behavior. The complete syndrome included spatial and temporal disorientation, psychomotor disturbance, change in affect and personality organization, alterations in the use of language and, in some cases, hallucinations. Anosognosia does not appear to be wholly explicable on the basis of a localized defect or a disruption of "body scheme." It may be better described as the manifestation of the patient's desire to be well, appearing in a new pattern of organization in the damaged brain.

Correlation of Clinical and EEG Abnormalities in Tumors and Vascular Disease of the Brain.

E. A. WEINSTEIN, R. L. KAHN AND H. STRAUSS. Tr. Am. Neurol. A., 75: 277, 1950.

The disturbance in behavior of 40 patients with tumors and vascular disease of the brain, in whom the EEG showed bilateral delta abnormalities, was compared with a group of 35 patients in whom the EEG abnormalities were unilaterally focal. Certain alterations of behavior occurred in all but 2 cases of the group with bilateral abnormality but were only rarely present with a focal abnormality. These included spatial and temporal disorientation, a paraphasic language disorder and a change in mood or personality. Incontinence and denial of illness were found only with bilateral abnormality. Aphasia, apraxia, finger agnosia, left-right disorientation, dyscalculia and memory loss occurred with the same frequency in both groups.

BOOK REVIEW

Annual Report on Stress (1951). BY SELYE, HANS. Acta, Inc. Montreal, Canada.

The publication of Hans Selye's first Annual Report, or supplement, on Stress, within a year of the appearance of the initial monumental work of 1950, testifies to the vast interest and impressive research that have been stimulated throughout the scientific world. Although the author, in the introduction, frankly admits, and even quotes, some of the criticisms that have been levelled against his almost all-embracing theories of the General Adaptation Syndrome (G-A-S) and the Alarm Reaction, the great bulk of scientific opinion appears to be deeply impressed with his conclusions, and especially their therapeutic utilization. Selye and his many collaborators have collected and carefully analyzed over 3000 references to the Stress Syndrome published in the year ending August, 1951. This voluminous literature emphasizes the vital role of the hypophysis-adrenal system in health and disease and the practical utilization of ACTH and Cortisone in therapy. The volume, almost identical in appearance with its distinguished predecessor, is attractively printed and illustrated, and is conveniently arranged both for reference and thorough perusal.

S. S. B.

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CONTENTS

NEWER KNOWLEDGE OF HUMAN BLOOD FACTORS. <i>Richard E. Rosenfield, M.D. and Peter Vogel, M.D.</i>	89
THE METABOLISM OF THE HUMAN HEART IN VIVO. <i>R. J. Bing, M.D.</i>	100
ATHEROSCLEROSIS: A PROBLEM IN NEWER PUBLIC HEALTH. <i>Ancel Keys, M.D.</i>	118
METACHRONOUS CARCINOMAS OF THE DUODENUM AND THE COLON. <i>Gerson J. Lesnick, M.D.</i>	140
BILATERAL TEMPOROMANDIBULAR ANKYLOSIS. <i>Leo Stern, Jr., D.D.S., Gabriel P. Seley, M.D., and Norman Cranin, D.D.S.</i>	145
REVELATIONS FROM THE EARLY ANNUAL REPORTS OF THE MOUNT SINAI HOSPITAL. <i>Joseph Hirsh, Ed. D.</i>	151

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NEWER KNOWLEDGE OF HUMAN BLOOD FACTORS*†

RICHARD E. ROSENFELD, M.D., AND PETER VOGEL, M.D.

In the past ten years a voluminous literature has accumulated concerning human blood types. The subject has overlapped into many sciences and has become difficult to understand even for those actively engaged in the specialty.

The blood factors are cell antigens in the stroma of erythrocytes. Singly or in combination they are termed agglutinogens because they combine with specific antibodies called agglutinins to produce the phenomenon of agglutination. The exact mechanism of antigen-antibody union is not clearly understood. However we know that antigen molecules combine with many molecules of antibody whereas antibody molecules combine with probably not more than two antigen molecules (1). The capacity of an antibody molecule to combine with the agglutinogens of two different erythrocytes results in the random aggregation of red cells termed agglutination.

Some agglutinogens are not confined to red cells but may be found in solution in the body fluids: e.g., ABO mucopolysaccharides (2), Lewis substances (3). Substances foreign to the body may greatly resemble agglutinogens on chemical analysis and may cross-react with hemagglutinating antibody: e.g., type XIV pneumococcus polysaccharide, anthrax polysaccharide, and blood group A substance (4).

All hemagglutinating agents are not antibodies. Certain chemicals have a potent hemagglutinating action: e.g., salts of heavy metals, colloidal silicic acid (5). Lima bean extracts contain a globulin which specifically agglutinates A₁ red cells (6, 7).

Serum agglutinins are globulins which are believed to develop as a result of antigen stimulation from specific parenteral blood or from cross-reacting foreign substances such as Forsmann antigen (8) or type XIV pneumococcus polysaccharide (4). When the source of stimulation is not evident the term *natural* antibody has been used (5). Depending upon the source of the red cells with which they react, agglutinins are divided as follows: 1. *Hetero-agglutinins*: reacting with red cells of another species. 2. *Iso-agglutinins*: reacting with red cells of the same species. 3. *Auto-agglutinins*: reacting with red cells of the individual producing the antibodies as well as with the red cells of all other members of the same species (*pan-agglutinins*).

Red cells may remain unagglutinated in the presence of specific antibody (9). This non-occurrence of agglutination may be due to either an agglutinin that is inaccessible (10) or an agglutinin that does not combine with more than one

* From the Blood Bank of The Mount Sinai Hospital and The Rh Laboratory, Bureau of Laboratories, Department of Health, City of New York.

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red cell (11, 12). The inaccessible or ill-functioning agglutininogen may be termed a *weakly reacting* blood factor (13). A non-agglutinating agglutinin has been termed an *incomplete* (11) or *univalent* (12) antibody. When an incomplete antibody can prevent the action of a known agglutinin of the same specificity, the term *blocking* (12) antibody is used. When red cells combine with antibody and remain unagglutinated, they are said to be *sensitized*.

There are a number of methods for detecting *sensitization* of red blood cells:

1. If sufficient complement is added to the system, and the antibodies are of the *complement-fixing* variety, lysis of the red cells will take place at 37°C. Under these circumstances the agglutinin is termed an *hemolysin* (*hetero-, iso-, or auto-hemolysin*, as circumstances warrant). Most human iso-agglutinins are so poorly complement-fixing that this technic is of little clinical value.

2. If certain hydrophilic colloids (e.g., plasma, serum, Fraction V albumin, acacia, gelatin, dextran, PVP) are present in optimal concentration, clumping of the sensitized red cells occurs (14, 15). This phenomenon has been termed *conglutination* (16). The method cannot be applied in some clinically important instances of iso-sensitization.

3. If red cells are treated optimally with certain proteolytic enzymes (e.g., trypsin, papain, ficin), they become agglutinable by certain so-called "incomplete" antibodies (17). This phenomenon may be dependent upon the exposure of more agglutininogen to the "outer effective limit" (10) of the red cell surface. Enzyme treatment destroys some agglutinogens, and is not helpful for the study of many others (18).

4. Red blood cells sensitized with human antibody may be agglutinated by the serum of a rabbit that has been previously immunized with human globulin (19). This is known as the antiglobulin test, and it is the most valuable technic available today for detecting both weakly reacting blood factors and incomplete antibodies (20). Rarely, a sensitizing antibody may be removed from the red cell surface by antiglobulin serum, so that even this test has limitations (20).

With but one exception, Le^a (and this may be only an expression of weak sera), all of the human blood factors are inherited as simple Mendelian characters (21). That is, the presence or absence of a factor is determined by the presence or absence of a particular gene at a particular locus on a particular set of one of the 24 pairs of chromosomes. One chromosome of a pair is derived from one parent while the opposite chromosome comes from the other parent. Thus, any factor present in a child must be present in one or both parents; furthermore, any factor present homozygously (on both chromosomes) in either parent must be present in all offspring, and any homozygous factor in a child must be present in both parents. There are important medico-legal applications of these facts.

It is possible to identify 10 of the 24 pairs of chromosomes in all humans. Nine of these ten are identified by means of blood typing.

In addition to the genetic implications of the blood types, important anthropological considerations are raised by the variations in frequency of the different

blood types in segregated populations. This is clearly illustrated by Table I which lists the frequencies of some blood types in Caucasians, Chinese, and Negroes of New York City (22).

TABLE I
*Comparative incidence of the blood factors of various racial groups**

SYSTEM	TYPES	CAUCASIANS	CHINESE	NEGROES
O-A ₁ -A ₂ -B	O	43.8	45.6	50.0
	A ₁	30.4	27.2	15.0
	A ₂	8.6	0.0	7.0
	B	12.6	22.3	23.5
	A ₁ B	3.4	4.9	2.5
	A ₂ B	1.2	0.0	2.0
M-N-S	M.S	20.8	3.9	6.9
	Mss	7.5	35.0	17.2
	MNS	26.7	5.8	16.6
	MNss	22.7	37.9	33.1
	NS	7.2	1.0	26.0
	Nss	15.1	16.5	20.2
P	P+	77.0	27.2	95.0
	P-	23.0	72.8	5.0
Rh-Hr	rh	14.4	1.0	5.5
	Rh ₁ Rh ₁	19.5	53.4	2.0
	Rh ₁ rh	31.5	11.7	24.5
	Rh ₂	16.3	8.7	16.0
	Rh ₁ Rh ₂	14.4	24.2	5.0
	Rh ₀	2.5	1.0	46.5
	rh'	1.0	0.0	0.5
	rh''	0.4	0.0	0.0
K-k	KK	0.3	0.0	3.5
	Kk	9.9	0.0	
	kk	89.8	100.0	
Fy	Fy ^a +	66.0	99.0	26.0
	Fy ^a -	34.0	1.0	74.0
Jk	Jk ^a +	77.8	55.0	90.5
	Jk ^a -	22.2	45.0	9.5
Lu	Lu ^a +	8.0		
	Lu ^a -	92.0		
Le	Le ^(a+b-)	22.8	23.5	23.0
	Le ^(a-b+)	71.5	70.6	61.0
	Le ^(a-b-)	5.7	5.9	16.0

* Modified from Table I, reference 22 with additions.

There are 23 clinically useful blood factors now identifiable. These are divided into 9 genetically independent systems. The 23 blood factors are not of equal importance. Some are identifiable by very weak iso-antibodies and require expert technic; e.g., Le^a, Le^b, P, Lu^a. Others are identifiable with sensitizing iso-antibodies that require the indirect antiglobulin test; e.g., Fy^a, K, Jk^a. Some

factors are known only through a few examples of iso-sensitization and there is insufficient serum available for their widespread usage: e.g., Jk^a, S, s, k, Lu^a, rh^a, hr^a.

A series of other blood factors have been described (21, 23). These are characterized by the universal (99.9+ %) presence or absence of the factor in the red cells of everyone except the propositus and, possibly, near relatives. These factors, thus far, appear to be genetically independent of each other and independent of the more useful blood factors.

THE ABO BLOOD GROUP FACTORS

There have been two important advances in the subject of the ABO blood groups: 1) the chemical isolation of A and B mucopolysaccharides, and 2) the recognition of A-B hemolytic disease of the newborn.

A and B mucopolysaccharides. Soluble mucopolysaccharides reacting specifically with anti-A and anti-B antibodies have been isolated from both human and animal sources (4). With these substances it has been possible to apply the highly critical analytical methods of immunochemistry to study the A and B factors and their specific antibodies. The usefulness of O substance (similar polysaccharide failing to react with either anti-A or anti-B but inhibiting anti-O sera) is limited because potent anti-O sera are not available. From studies of these substances and their specific antibodies, it has been suggested that the ABO factors may be further complicated by the occurrence of an *H* factor from which the A, B, and O factors arose as mutations (24). Partial confirmation of this hypothesis has been the finding of 3 individuals whose red cells typed with anti-A and anti-B sera as group O but whose sera contained inhibitable anti-O antibodies. Thus a situation was created wherein the three individuals were mutually compatible on cross-match but incompatible with all other group O bloods (25).

Clinically, these substances have had three applications: 1) Because of their antigenicity, they have been used for the stimulation of donors for the production of extremely potent grouping sera (26). 2) As *in vitro* neutralizing agents for anti-A and anti-B antibodies, the polysaccharides have aided in the preparation of anti-Rh and other typing serums (27). 3) The polysaccharides have been added to Group O blood for "universal" donation (i.e., to overcome the "minor" incompatibility) (27).

A-B Hemolytic Disease of the Newborn. Group incompatible pregnancy (serum of mother vs. red cells of fetus) has a frequency of 25 %. A number of studies have shown that this situation is associated with a low incidence of fetal death and neonatal hemolytic disease directly attributable to the incompatibility (28). Obviously, the mortality due to this disease cannot be great or it would have an effect on the blood group frequencies of a population through loss of individuals of groups A, B, and AB.

Unfortunately, it is not possible to detect in advance which mothers may deliver infants with this disease. There may be some degree of correlation with high titer anti-A and anti-B antibodies in the mother, especially incomplete

antibodies. Peculiarly, the red cells of the involved babies do not appear to be as strongly sensitized with antibody as in Rh disease: The direct antiglobulin test varies from negative to weak positive and must be performed with great care to avoid a false negative result since the sensitizing antibody appears to be loosely bound to the red cell (20).

Blood films taken soon after birth in moderately severe cases are very striking because of the presence of 5-20 % spherocytes (29). The spherocytosis is not distinguishable from that seen in other varieties of spherocytic hemolytic anemia but is quite different from the almost uniform macrocytosis encountered in Rh disease.

Only about 1 case in 20 is severe enough to require treatment. Simple anemia is easily handled with the transfusion of packed group O red cells. Severe jaundice should be handled by exchange transfusion with group O blood. Kernicterus and death are rarely encountered.

Transfused group O red cells have been shown to survive normally in A-B hemolytic disease of the newborn, whereas transfused red cells of homologous group, given simultaneously, have been shown to be preferentially destroyed at a very rapid rate (30).

THE Rh-Hr FACTORS

As a cause of hemolytic transfusion reactions and of hemolytic disease of the newborn, this system accounts for most of our difficulties. The Rh₀ antigen must be considered fairly potent since it is estimated that 50-75 % of Rh negative individuals can be immunized with adequate stimulation over a long enough period of time (31). Although the subfactors are not of as much clinical importance, many examples of iso-immunization have been recorded.

Sera are available today to define the following Rh-Hr factors: Rh₀(D), rh'(C), rh"(E), rh^w(C^w), hr'(c), and hr"(e). Regardless of specificity, all of the Rh-Hr agglutinins behave similarly if the sera are of sufficient potency: they may be saline agglutinin or incomplete, and when incomplete, agglutination may be produced with the use of hydrophilic colloids (particularly bovine albumin), enzyme treated red cells, and the antiglobulin test.

There are several peculiarities about the Rh-Hr factors. 1) Weakly reacting variants are fairly common, particularly in Negro populations, and constitute a serious typing problem for the Rh₀ factor (13). 2) Most sera, except anti-Rh₀, show a dosage effect: better avidity with homozygous red cells than with heterozygous red cells (21). 3) The red cell, Rh₂Rh₀ (Rh₁Rh₂) (CDe/cDE), appears to contain less rh'(C), rh"(E), hr'(c), and hr"(e) than other red cells heterozygous for these factors: e.g., Rh₁rh (CDe/cde) and Rh₂rh (cDE/cde) (32). 4) There is some evidence for cross-reactivity between Rh₀(D) and rh'(C), and there may be lesser cross-reactivity between some other Rh-Hr factors such as hr'(c) and rh"(E) (33). We have observed six instances of acquired hemolytic anemia where a pan-agglutinin in the serum of the patient reacted much more strongly with red cells containing the rh"(E) factor. This may not be too remarkable since anti-rh" is the only Rh-Hr antibody to come to our attention as rarely

being of "natural" origin (two instances were unassociated with other antibodies, and a third was associated with natural anti-S).

There has been a great deal of controversy about the nomenclature and genetics of the Rh-Hr system. This resulted from the rapidity with which new factors were discovered (necessitating rapid changes in nomenclature) and a break in communications between American and English serologists during World War II. The English workers state that the facts are best expressed by the concept of three linked multiply allelic genes (34) with rare cross-over (not thus far demonstrated), whereas Wiener has insisted that a single multiply allelic locus best expresses the facts (35).

THE M-N-S-s FACTORS

The M-N-S-s system promises to be one of the most interesting of the human blood group systems.

The original M-N system consists of two allelic factors, M and N, defined by reagent fluids obtained from the sera of rabbits immunized with either M or N red cells (36). These typing fluids are of great importance 1) in medico-legal problems (37), 2) in survival determinations of transfused red cells (38), and 3) in human genetic and anthropologic studies (39).

S⁴⁰ and s⁴¹ are different factors that are genetically linked (on the same chromosome) with the M and N factors. They, too, may be considered as a separate double allele system. However, since cross-over has not been observed thus far, it is much more interesting to consider the combination of closely or completely linked double alleles, where every M and N factor is either S positive or s positive. This consideration yields a system of 10 genotypically distinct bloods, instead of 6, and because of the incidence of the factors, offers an opportunity for distinguishing bloods that is more efficient than the Rh-Hr system (21).

The M, N, S, and s factors are only feebly antigenic in man. Natural anti-M and anti-N agglutinins are easily recognized since their potency is greatly reduced at 37°C. and since the M and N factors are destroyed by the usual proteolytic enzyme treatment of red cells. Anti-S is a similar type of agglutinin, although the factor, S, is potentiated by routine trypsin treatment. There is only one example of anti-s, and the serum is weak; the factor, s, is also potentiated by trypsin treatment. The M-N-S-s antibodies that function at 37°C. may cause transfusion reactions and hemolytic disease of the newborn (42, 43, 44). When the M-N-S-s antibodies are of the incomplete variety, they are best demonstrated by the antiglobulin test.

THE Le (LEWIS) FACTORS

Although of little clinical interest except as a possible cause of some febrile transfusion reactions, the Lewis system has aroused our recent interest (45). Because of the implications of the peculiarities we have found, more discussion will be given this subject than is otherwise warranted.

There are two Lewis antisera, anti-Le^a (46) and anti-Le^b (47). Both antibodies are naturally occurring. In adults, anti-Le^a agglutinates only those red cells

homozygous for the factor, whereas anti-Le^b agglutinates both heterozygotes and homozygotes and does not show dosage effect. Otherwise the behavior of these antibodies is identical and the characteristics may be listed as follows:

- 1) Both antibodies work best at lower temperatures but are active at 37°C.
- 2) Both antibodies are complement-fixing and, when sufficiently potent, lyse red cells at 37°C. in the presence of human complement. The presence of human complement inhibits agglutination.

The Le^a and Le^b factors are also unusual. They are water-soluble and may be demonstrated in the supernatant saline of washed red cells on standing (48). They are present in all the body fluids, particularly saliva, of individuals possessing the factors (49). When red cells are treated with enzyme, the Le factors are enhanced for both the agglutination and the hemolytic phenomena (18). Some individuals are deficient in Lewis substance in their red cells but possess a small amount in the saliva; a few individuals are devoid of Lewis substance entirely (45). The Lewis blood type is identical with the A-B-O secretor status of an individual—all Le^a positives are non-secretors whereas all Le^b positives are secretors (50, 45). This relationship between Lewis and A-B-O secretor status is constant even for individuals deficient in Lewis substance but having enough to entirely, anti-Le^a is frequently present in the serum as a natural antibody (45). When the serum is even of moderate potency, anti-Le^b is also present (45). In A-B-O non-secretors of groups A₁, B, and A₁B, when devoid of Le^b substance anti-Le^b frequently occurs in the serum as a natural antibody. Almost invariably anti-O is also present (45). When the anti-O is the predominant antibody, the anti-Le^b fails to agglutinate any bloods of groups A₁, B, or A₁B; but if the anti-O is weak, the anti-Le^b is usable with bloods of any group (45). The anti-Le^b antibody accompanying anti-Le^a similarly reacts only with bloods of groups O and A₂ (45).

THE Fy^a-Fy^b (DUFFY) FACTORS

Immunization to the Fy factors is not common but is becoming better recognized as an occasional cause of hemolytic transfusion reaction and hemolytic disease of the newborn.

Numerous examples of Fy^a immunization have been described (51). In all instances, the antibodies could be demonstrated only by the indirect antiglobulin test, and failed to agglutinate red cells in any other manner, although one example (52) did contain a very weak (1:1) saline agglutinin. All examples sensitize red cells best at 37°C. The first case of immunization to Fy^a encountered at The Mount Sinai Hospital was one of the most unusual described (53). The antibody appeared to be of natural origin, but was responsible for a mild reaction at the time of the patient's very first blood transfusion. It is no longer unusual to detect anti-Fy^a antibodies in sera containing potent anti-Rh antibodies.

The Fy^a factor is partially destroyed by routine enzyme treatment of red cells (18).

Immunization to Fy^b has been described only recently. It was the cause of hemolytic disease of the newborn (54). The antibody was a weak saline agglutinin

reacting much better in the presence of hydrophilic colloids, especially gelatin and bovine albumin. Reactions were best at 37°C.

THE K-k (KELL) FACTORS

Immunization to the K factor (55) has been responsible for severe hemolytic disease of the newborn and severe transfusion reactions. As an antigen the K factor is probably as potent as hr'. Immunization to K is seen occasionally in conjunction with immunization to the Rh₀ and hr' factors.

Although one weak saline agglutinin of anti-K has been described (56), all the other examples have been incomplete. The antigen-antibody reaction is optimal at 37°C. Red cells sensitized with anti-K can be agglutinated weakly with bovine albumin, but the indirect antiglobulin test usually gives much more clear-cut results.

Routine enzyme treatment of red cells does not destroy the K factor but does not usually potentiate agglutination (18).

Immunization to k is very rare (57, 58). This is to be expected since only about 2 individuals in 1000 lack the antigen. The antibodies are warm saline agglutinins. Agglutination is not potentiated by the use of hydrophilic colloids, trypsin treatment of red cells, or the indirect antiglobulin test. Routine trypsin treatment does not destroy the k factor. Although only two examples of immunization have been described, one was responsible for hemolytic disease of the newborn and the other occurred after multiple blood transfusions.

THE Jk^a (KIDD) FACTOR

Immunization to the Jk^a factor has been responsible for hemolytic transfusion reaction (59) and possibly hemolytic disease of the newborn. We have observed two examples in pregnancy. In one, the antibody response accompanied a high titer anti-Rh antibody, while in the other it was pure and possibly the result of a single blood transfusion (60). The antibodies function best at 37°C. and can be demonstrated only by the indirect antiglobulin test. Routine trypsin treatment appears to partially destroy the agglutinin.

THE P FACTOR

A cold agglutinin with P specificity is frequently observed in P negative individuals (61). The agglutinin is weakly antigenic to rabbits and negligibly so to humans (38). When sufficiently potent, the natural sera agglutinate all P positive red cells similarly, but the much more common weak examples give three degrees of positivity (62). Routine trypsin treatment potentiates the P factor (18).

The factor is clinically unimportant except as a cause of troublesome cross-matches.

THE Lu^a (LUTHERAN) FACTOR

Several examples of anti-Lu^a (60) have been found in England. The antibodies are extremely weak and the degree of agglutination obtained with the lyophilized

material we have studied is so poor that our routine methods may be overlooking other examples. The antibodies are saline agglutinins and the reaction is not potentiated by hydrophilic colloids, trypsin treatment of red cells, or the indirect antiglobulin test.

SUMMARY AND CONCLUSIONS

1. Some of the newer concepts of the antigen-antibody reaction in human isoagglutination are briefly discussed.

2. The application of the various blood group systems in clinical medicine are presented.

ADDENDUM

Since this paper was submitted, isoantibodies defining two new blood factors have been found. One antibody has the specificity predicted for anti-Jk^b and thus fully establishes the Jk (Kidd) factors as allelic Mendelian characters (Plant, G., Ikin, E. W., Mourant, A. E., Sanger, R., and Race, R. R. A New Blood Group Antibody; Anti-Jk^b. *Nature*, 171: 431, 1953). The other antibody defines a new blood factor in the Rh-Hr series which appears to be distinct from the D-d, C-c, and E-e alleles of the English workers, and has therefore been termed f (Rosenfield, R. E., Vogel, P., Gibbel, N., Sanger, R., and Race, R. R., *Brit. Med. Jour.*, 1: 975, 1953. Work is in progress to further define the f factor, and to discover an antibody for the expected allelic factor F.

BIBLIOGRAPHY

1. MARRACK, J. R., HOCH, H., AND JOHNS, R. G. S.: The Valency of Antibodies. *Brit. J. Exper. Path.*, 32: 212, 1951.
2. SCHIFF, F.: Über gruppenspezifische serumpräcipitine. *Klin. Wehscr.*, 1: 679, 1924.
3. BRENDAMOEN, O. J.: Studies of Agglutination and Inhibition in Two Lewis Antibodies. *J. Lab. & Clin. Med.*, 34: 538, 1949.
4. KABAT, E. A. AND MAYER, M. M.: *Experimental Immuno-chemistry*. Springfield, Ill., Chas. C Thomas, 1948, p. 567.
5. LANDSTEINER, K.: *The Specificity of Serological Reactions*. Cambridge, Mass., Harvard University Press, 1945, p. 310.
6. BOYD, W. C. AND RIGUERA, R. N.: Hemagglutinating Substances for Human Cells in Various Plants. *J. Immunol.*, 62: 333, 1949.
7. ROSENFELD, R. E., VOGEL, P., AND HABER, G.: Unpublished observations.
8. SCHIFF, F. AND ADELSBERGER, L.: *Ztschr. f. Immunitätsforsch. u. exper. Therap.*, 40: 335, 1924.
9. DIAMOND, L. K.: Progress report to committee on Medical Research of the Office of Scientific Research and Development. O E M cmr. 384, 1944.
10. COOMBS, R. R. A., GLEESON-WHITE, M. H., AND HALL, J. G.: Factors Influencing the Agglutinability of Red cells. II. The Agglutination of Bovine Red Cells Previously Classified as Inagglutinable by the Building Up of an Anti-Globulin: Globulin Lattice on the Sensitized Cells. *Brit. J. Exper. Path.*, 321: 195, 1951.
11. RACE, R. R.: An Incomplete Antibody in Human Serum. *Nature*, 153: 771, 1944.
12. WIENER, A. S.: A New Test (Blocking Test) for Rh Sensitization. *Proc. Soc. Exper. Biol. & Med.*, 56: 173, 1944.
13. ROSENFELD, R. E., VOGEL, P., MILLER, E. B., AND HABER, G.: Weakly Reacting Rh Positive (D⁺) Bloods. *Blood*, 6: 1123, 1951.

14. DIAMOND, L. K. AND ABELSON, N. M.: The Demonstration of Anti-Rh Agglutinins, an Accurate and Rapid Slide Test. *J. Lab. & Clin. Med.*, 30: 204, 1945.
15. ——— AND DENTON, R. L.: Rh Agglutination in Various Media with Particular Reference to the Value of Albumin. *J. Lab. & Clin. Med.*, 30: 821, 1945.
16. WIENER, A. S.: Conglutination Test for Rh Sensitization. *J. Lab. & Clin. Med.*, 30: 662, 1945.
17. MORTON, J. A. AND PICKLES, M. M.: Use of Trypsin in the Detection of Incomplete Anti-Rh Antibodies. *Nature*, 159: 779, 1947.
18. ROSENFELD, R. E. AND VOGEL, P.: The Identification of Hemagglutinins with Red Cells Altered with Trypsin. *Tr. New York Acad. Sci.*, 13: 213, 1951.
19. COOMBS, R. R. A., MOURANT, A. E., AND RACE, R. R.: Detection of Weak and 'Incomplete' Rh Agglutinins; a new test. *Lancet*, 2: 15, 1945.
20. ROSENFELD, R. E., VOGEL, P., AND ROSENTHAL, N.: The Antiglobulin Test. *Am. J. Clin. Path.*, 4: 301, 1951.
21. RACE, R. R. AND SANGER, R.: *Blood Groups in Man*. Oxford, England, Blackwell, 1950, p. 290.
22. MILLER, E. B., ROSENFELD, R. E., AND VOGEL, P.: On the Incidence of Some of the New Blood Agglutinogens in Chinese and Negroes. *Am. J. Phys. Anthropol.*, 9: 115, 1951.
23. LEVINE, P.: A Brief Review of the Newer Blood Factors. *Tr. New York Acad. Sci.*, 13: 205, 1951.
24. MORGAN, W. T. J. AND WATKINS, W. M.: The Detection of a Product of the Blood Group O Gene and the Relationship of the 50 Called O Substance to the Agglutinogens A and B. *Brit. J. Exper. Path.*, 29: 159, 1948.
25. BHENDE, Y. M., DESHPANDE, C. K., BHATIA, H. M., SANGER, R., RACE, R. R., MORGAN, W. T. J., AND WATKINS, W. M.: A 'New' Blood Group Character Related to the ABO System. *Lancet*, 262: 903, 1952.
26. WITEBSKY, E., KLENDSHOJ, N. C., AND MCNEIL, E.: Potent Typing Sera Produced by Treatment of Donors with Isolated Blood Group Specific Substances. *Proc. Soc. Exper. Biol. & Med.*, 55: 167, 1944.
27. ———: Isolation and Purification of Blood Group A and B Substances; Their Use in Conditioning Universal Donor Blood, in Neutralizing Anti-Rh Sera, and in The Production of Potent Grouping Sera. *Ann. New York Acad. Sci.*, 46: 887, 1946.
28. WIENER, A. S., WEXLER, I. B., AND HURST, J. G.: The Use of Exchange Transfusion for the Treatment of Severe Erythroblastosis due to A-B Sensitization, with Observations on the Pathogenesis of the Disease. *Blood*, 4: 1014, 1949.
29. GRUMBACH, VON A. AND GASSER, C.: ABO-Incompatibilitaten und Morbus Haemolyticus Neonatorum. *Helvet. Paediatrica. Acta* 3: 447-474, 1948.
30. MOLLISON, P. L. AND CUTBUSH, M.: Hemolytic Disease of the Newborn due to Anti-A Antibodies. *Lancet*, 2: 173, 1949.
31. DIAMOND, L. K. AND ALLEN, F. M.: Rh and Other Blood Groups. *New England J. Med.*, 241: 867, 1949.
32. RACE, R. R.: Blood Groups and Their Inheritance with Particular Reference to the Rh and MN Systems. Delivered 2nd Congr. Internat. Soc. Hemat. Buffalo, N. Y., Aug. 1948.
33. ROSENFELD, R. E. AND VOGEL, P.: Unpublished observations.
34. FISHER, R. A.: Cited by Race, R. R. (11).
35. WIENER, A. S.: Genetic Theory of the Rh Blood Types. *Proc. Soc. Exper. Biol. & Med.*, 54: 316, 1943.
36. LANDSTEINER, K. AND LEVINE, P.: On the Inheritance of Agglutinogens of Human Blood Demonstrable by Immune Agglutinins. *J. Exper. Med.*, 48: 731, 1928.
37. WIENER, A. S.: *Blood Groups and Transfusions*. Springfield, Ill., Chas. C Thomas, 1943, p. 438.

38. MOLLISON, P. L.: *Clinical Aspects of Blood Transfusion*. Oxford, England, Blackwell, 1952, p. 350.
39. MOURANT, A. E.: *The Distribution of Blood Groups in Animals and Humans*. Oxford, England, Blackwell. In press.
40. WALSH, R. J. AND MONTGOMERY, C.: A New Human Isoagglutinin Subdividing the MN Blood Groups. *Nature*, 160: 504, 1947.
41. LEVINE, P., KUHMICHEL, A. B., WIGOD, M., AND KOCH, E.: A New Blood Factor, s, Allelic to S. *Proc. Soc. Exper. Biol. & Med.*, 78: 218, 1951.
42. WIENER, A. S.: Reaction Transfusionnelle Hemolytique due a une Sensibilisation Anti-M. *Revue d'Hematologie*, 5: 3, 1950.
43. CUTBUSH, M. AND MOLLISON, P. L.: Haemolytic Transfusion Reaction due to Anti-S. *Lancet*, 2: 102, 1949.
44. LEVINE, P., FERRARO, L. R., AND KOCH, E.: Hemolytic Disease of the Newborn due to Anti-S. A Case Report with a Review of 12 Anti-S Sera Cited in the Literature. *Blood*, 7: 1030, 1952.
45. MILLER, E. B., ROSENFELD, R. E., AND VOGEL, P.: The Lewis Factors in Negroes. In preparation.
46. MOURANT, A. E.: A New Human Blood Group Antigen of Frequent Occurrence. *Nature*, 158: 237, 1946.
47. ANDRESEN, P. H.: The Blood Group System L. A New Blood Group L₂. A Case of Epistasy within the Blood Groups. *Acta path. et microbiol. Scandinav.*, 25: 728, 1948.
48. BRENDAMOEN, O. J.: Cited by Race, R. R. and Sanger, R. (21).
49. ———: Studies of Agglutination and Inhibition in Two Lewis Antibodies. *J. Lab. & Clin. Med.*, 34: 538, 1949.
50. GRUBB, R.: Correlation between Lewis Blood Group and Secretor Character in Man. *Nature*, 162: 933, 1948.
51. CUTBUSH, M., MOLLISON, P. L., AND PARKIN, D. M.: A New Blood Group. *Nature*, 165: 188, 1950.
52. BROWN, IVAN: Personal communication.
53. ROSENFELD, R. E., VOGEL, P., AND RACE, R. R.: Un nouvel exemplaire d'anti-Fy^a dans serum humaine. *Revue d'Hematologie*, 5: 315, 1950.
54. IKIN, E. W., MOURANT, A. E., PETTENKOEFER, H. J., AND BLUMENTHAL, G.: Discovery of the Expected Haemagglutinin, Anti-Fy^b. *Nature*, 168: 1077, 1951.
55. COOMBS, R. R. A., MOURANT, A. E., AND RACE, R. R.: In Vivo Isosensitization of Red Cells in Babies with Haemolytic Disease. *Lancet*, 1: 264, 1946.
56. DUNSFORD, I.: A Saline Agglutinating Kell Antibody, *Nature*, 163: 962, 1949.
57. LEVINE, P., BACKER, M., WYGOD, M., AND PONDER, RUTH: A New Human Hereditary Blood Property (Cellano) Present in 99.8% of all Bloods. *Science*, 109: 464, 1949.
58. ———, KUHMICHEL, A. B., AND LOYGOD, M.: A Second Example of Anti-Cellano (Anti-k). *Blood*, 7: 251, 1952.
59. ALLEN, F. H., DIAMOND, L. K., AND NIEDZIELA, B.: A New Blood Antigen. *Nature*, 167: 482, 1951.
60. VOGEL, P., ROSENFELD, R. E., AND GIBBEL, N.: Three Further Examples of the Anti-Jk^a Antibody. In preparation.
61. LANDSTEINER, K. AND LEVINE, P.: Further Observations on Individual Differences of Human Bloods. *Proc. Soc. Exper. Biol. & Med.*, 24: 941, 1927.
62. MILLER, E. B., TANNOR, H. D., AND HSU, C.: The P Factor and Its Variants in Caucasians, Negroes, and Chinese. *J. Lab. & Clin. Med.*, 36: 230, 1950.
63. CALLENDER, S. T. AND RACE, R. R.: A Serological and Genetical Study of Multiple Antibodies Found in Response to Blood Transfusion by a Patient with Lupus Erythematosus Diffusus. *Ann. Eugenics*, 13: 102, 1946.

THE METABOLISM OF THE HUMAN HEART IN VIVO^{1,2,3}

R. J. BING, M.D.

*Professor of Experimental Medicine and Clinical Physiology, Medical College of Alabama,
Birmingham, Alabama*

Studies on cardiac metabolism, in the past, have been carried out mainly on artificial preparations in vitro (1-11). Physiologists preferred the heart lung preparation or the heart oxygenator system for these studies while the biochemists used heart homogenates or tissue slices (12-14). These in vitro studies have certain advantages over those carried out on the heart in situ. It is possible in the heart lung preparation to measure the concentration of any substance in the coronary arterial and venous blood as well as its concentration in the heart muscle. In experiments on heart tissue slices or homogenates the effect of interrupting selected enzyme systems on the cardiac metabolism may be studied. However, the in vitro studies are carried out in an artificial medium which has lost its continuity with the internal environment of the organism. Recent advances in technique have now made it possible to investigate certain phases of myocardial metabolism through the use of catheterization of the coronary sinus (15-19); the studies to be described deal with investigations which utilize this technique.

The coronary sinus is intubated to obtain coronary vein blood. It is not necessary to sample coronary arterial blood directly since the concentration of a substance is the same in peripheral arterial and coronary arterial blood. Coronary vein blood is collected through a catheter introduced through the arm vein and the right auricle into the coronary sinus. Details of this technique have been described (16). Once the catheter tip has entered the sinus it is possible to measure the coronary blood flow (16). Furthermore, coronary vein and peripheral arterial blood can be sampled simultaneously in order to obtain the myocardial extraction of a number of substances, including oxygen, electrolytes, and food-stuffs such as carbohydrates, fats, and proteins (20-27). The myocardial usage of these substances then may be calculated as the product of coronary flow times myocardial extraction.

One of our main purposes was the determination of the quantity of oxygen used in the aerobic combustion of any metabolite; consequently the oxygen extraction ratios of these substances were calculated as the ratios of their oxygen equivalent to the myocardial oxygen extraction. This oxygen extraction ratio represents the contribution of the aerobic catabolism of these substances to the total myocardial oxygen extraction. We may assume that, if the oxygen ex-

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² From the Depts. of Medicine and Physiology, Medical College of Alabama, Birmingham, Alabama.

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traction of a metabolite which is used in the aerobic cardiac metabolism is elevated, a large proportion of the energy taken in by the heart in the form of oxygen is used in the combustion of this substance. Conversely, if the oxygen extraction ratio is decreased, a smaller proportion of oxygen taken up by the heart is used in the aerobic metabolism of this compound. Admittedly, these statements have to be made with reservations as will be indicated later in this lecture.

We were particularly interested in the question: What is the efficiency with which the oxidative energy derived from the various foodstuffs is converted into cardiac work? None of the procedures generally used in chemical energetics seemed to be applicable. Furthermore, it is not possible to estimate accurately the weight of the heart or the left ventricular muscle; thus, it is impossible to apply equations in which the mechanical efficiency is expressed as the ratio of cardiac work of the left ventricle to the oxygen equivalent of the various foodstuffs extracted by this muscle. Consequently, we decided to forego any attempts to express energy transformations quantitatively and use instead an arbitrary ratio: the work of the left ventricle over the oxygen extraction ratios of the various foodstuffs. This ratio, the "energy conversion factor" represents only a comparative index of the contribution of oxidative energy derived from various metabolites to the useful work of the heart. By nature of this calculation, comparisons between the energy conversion of different metabolites are impossible; however, a lowering of the contribution factors suggests that a small proportion of the oxidative energy derived from this specific compound is converted into mechanical work; an elevation of the contribution factors may indicate a more effective conversion of the oxidative energy derived from this substance into useful work.

Our studies were carried out on a total of 70 patients, 9 of whom were in cardiac failure. Of these, 3 suffered from failure due to hypertensive heart disease and had a cardiac index less than 3 meters/sq. meter body surface area. The remainder had thyrotoxicosis with failure and a cardiac index ranging from 4 to 7 liters per sq. meter/minute. Of the patients who were not in cardiac failure, several had no evidence of heart disease, others had hypertensive cardiovascular disease, rheumatic valvular disease, congenital heart disease, thyrotoxicosis, A-V fistula or anemia.

Before dealing in detail with the individual phases of metabolism of the normal and failing human heart, I would like to stress that oxidation of foodstuffs, whether carbohydrates, fats, or proteins, to carbon dioxide and water for the provision of energy is not the sole factor in determining the myocardial extraction of these compounds. For example, an increase in myocardial glucose extraction may be the result of its conversion into glycogen. This is a strictly aerobic process, since the supply of energy rich phosphate bonds in ATP must be continuously replenished by oxidation. In this case, the oxygen extracted from the coronary blood would be used for storage and not for chemical energy. Eventually, heart muscle glycogen may be used for the provision of energy but it is doubtful whether this would lead to the formation of glucose as Cori has

shown (28). Only the last portion of glycogenolysis is aerobic, since from glycogen to the formation of pyruvic acid the anaerobic part of carbohydrate metabolism must be the major pathway (29). Consequently, we assume that the metabolic processes which we are studying are oxidative. This is probably a safe assumption; however we cannot be certain that the oxygen uptake by the heart, which we relate to the aerobic catabolism of the individual substances, is used only for energy production. Peters has stated that all 3 foodstuffs, fats, carbohydrates, and proteins, have an operative as well as an energy producing function (30). All this is mentioned in order to emphasize that the methods which are described in this lecture do not permit any conclusions on the metabolic pathway within the heart muscle cell. We see only the overall result of these intermediary processes.

In dealing first with the oxidative myocardial metabolism, we notice, as described in previous publications, that the heart when faced with a normal load, extracts a considerable, almost maximal, amount of oxygen from the blood; this quantity is even greater than that extracted by working skeletal muscle. Because of the large oxygen extraction, the first line of defense of the heart against increased metabolic demand lies in an increase in the coronary blood flow. It is clear that if there is any impediment to the flow of blood into the heart muscle, this line of defense is broken with the resulting disastrous effects of myocardial ischemia and anoxemia.

In low output failure the major change is a reduction in the cardiac output and, consequently, a diminution in cardiac work. However, there is no change in the oxygen consumption of the heart and, therefore, the fall in efficiency is primarily the result of the diminution in the cardiac work. The heart appears to have lost, in part, its ability to convert aerobic energy into useful work. This finding is in disagreement with results obtained on the heart lung preparation where, in acute failure, the myocardial oxygen consumption rises as the diastolic volume of the heart increases (4). In the human heart, therefore, a chronic increase in cardiac load is not commensurate with increased oxygen consumption. However, when the failing heart, which has already been exposed to long periods of chronic stretch, is subjected to further acute changes in load causing a further increase in the diastolic volume, such as occurs during exercise, its oxygen consumption rises just as it increases in acute failure (Fig. 1). However, in contrast to the normal heart, increased load results in a diminution in myocardial efficiency as a result of a relatively large increase in the oxygen consumption occurring concomitantly with a smaller increase in the work of the heart (Fig. 1). This illustrates again the difference in the response of the myocardium to an acute and chronic increase in load.

We shall now turn our attention to the metabolism of carbohydrates in the nonfailing human heart *in vivo*. A number of processes involving glucose can take place in the heart muscle cell (Fig. 2). Glucose can be converted to glycogen, fats, or proteins. We are unable, with our method, to relate the difference in the glucose concentration between coronary arterial and venous blood to any of these specific processes. However, certain features of glucose metabolism be-

come apparent. For example, the heart of individuals who have been fasting for 12 hours, or who have had a meal containing some carbohydrates prior to the

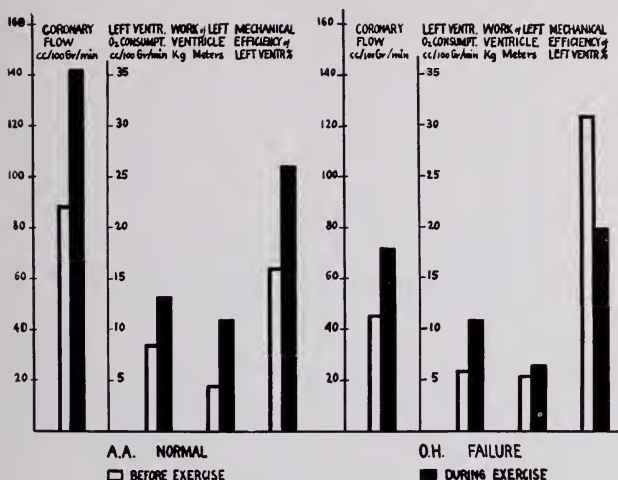


FIG. 1. The response of the coronary circulation, left ventricular oxygen consumption and work, and the mechanical efficiency of the left ventricle to increased load. Since, in failure the left ventricular oxygen consumption increases more than the work of the left ventricle, the mechanical efficiency of the left ventricle decreases.

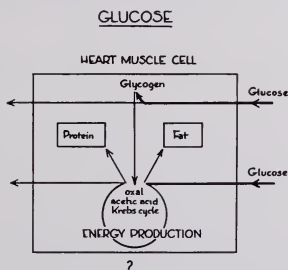


FIG. 2. Possible metabolic pathways of glucose in the heart muscle cells.

test, takes out only small amounts of glucose when the arterial glucose concentration is below 80 mg. % (Fig. 3). As the arterial glucose concentration increases, the extraction rises rapidly until, at blood concentrations of above 110 mg. %,

the extraction of glucose appears to have reached its maximal values. A similar relationship exists between arterial glucose concentration and myocardial usage of glucose (Fig. 4). Apparently the relationship between glucose extraction and arterial glucose concentration is a function of the logarithm of the arterial glucose concentration (Fig. 5).

The situation is different when the arterial blood glucose concentration is suddenly raised as the result of intravenous infusion of glucose (Fig. 6). Under these circumstances, an upper limit of glucose extraction seems to be absent. It is likely that the heart, when confronted with a sudden increased glucose load, uses sugar not only for oxidative processes but probably also for storage in the form of glycogen. It is possible that the balance between glycogen formation

MYOCARDIAL GLUCOSE EXTRACTIONS AT STEADY ARTERIAL GLUCOSE CONCENTRATION (Semi-log)

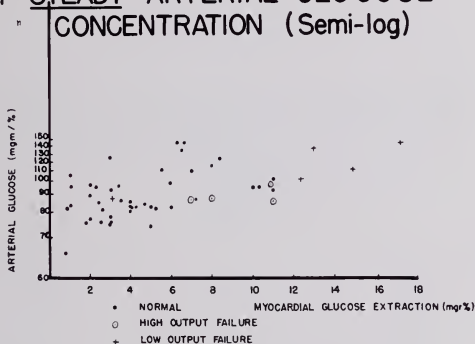


FIG. 5. The myocardial glucose extraction is a function of the logarithm of the arterial glucose concentration.

and oxidation of glucose in the heart is similar to that which occurs in the body as a whole during the injection of glucose. It has been shown by Butsch that as the quantity of glucose injected increased, a relatively large proportion retained went to form glycogen (31). Glycogenesis did not diminish as rapidly as oxidation. It is likely that, in the human heart in vivo, both storage and combustion of glucose vary directly with the blood sugar up to the limit of the myocardium to utilize sugar. This limit is probably fixed by the capacity to store sugar and by the total energy production of the heart. During infusion of glucose the amount of oxygen which can be accounted for by its catabolism is greatly increased and the contribution of the combined catabolism of glucose, lactate and pyruvate to the aerobic metabolism of the heart more than doubles in the majority of these

MYOCARDIAL GLUCOSE EXTRACTION DURING GLUCOSE INFUSION.

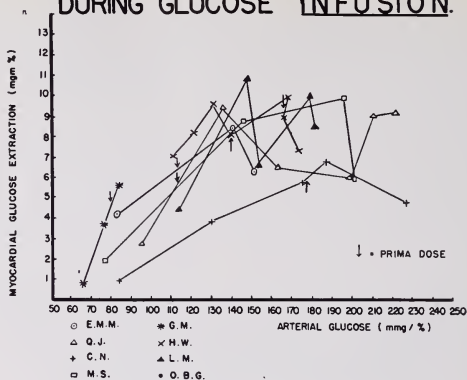


FIG. 6. Intravenous infusion of a 10% glucose solution results in increasing myocardial glucose extraction regardless of the height of the arterial blood glucose concentration.

TOTAL CARBOHYDRATE EXTRACTION RATIOS BEFORE AND DURING GLUCOSE INFUSION

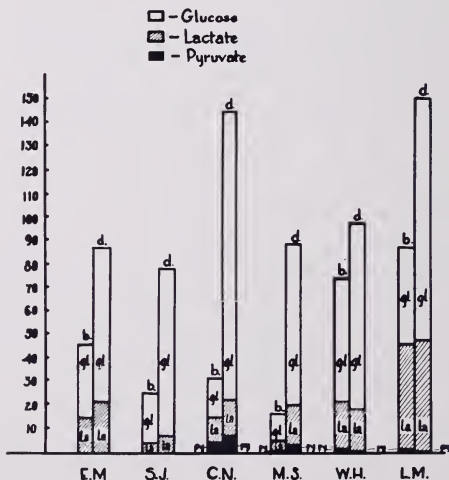


FIG. 6a. The contribution of the aerobic metabolism of carbohydrates to the oxygen extraction of the heart before and during glucose infusion. The amount of oxygen accounted for by the catabolism of glucose is increased during infusion.

tests (Fig. 6a). This, as I have indicated, may be the result of increased glycogenesis or energy metabolism.

It has been known for a great number of years that in contrast to skeletal muscle, heart muscle can utilize lactate and that lactate is important in the energy production of the heart (32). Lactate may be converted to glycogen or

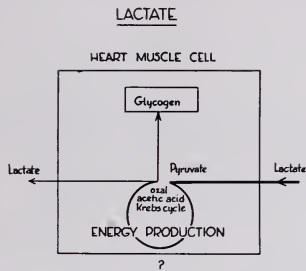


FIG. 7. Possible metabolic pathways of lactate in the heart muscle cell.

MYOCARDIAL LACTATE EXTRACTIONS AT STEADY ARTERIAL GLUCOSE CONCENTRATIONS

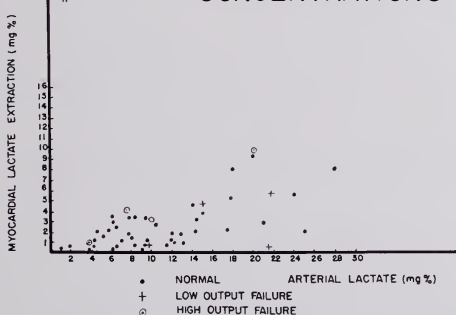


FIG. 8. The effect of spontaneous variations in arterial lactate concentration on myocardial lactate extraction. A rise in arterial lactate concentration leads to increased myocardial lactate extraction.

it may be shunted through the Krebs cycle, thus being used for energy production (Fig. 7). Although our methods do not permit any conclusions as to which of these pathways are followed, we do know that lactate is used by the heart. A rise in arterial lactate level is followed by increased myocardial lactate extraction and by an increase in myocardial lactate usage (Fig. 8). In this respect, at

least, glucose and lactate appear to be handled by the myocardium in a similar fashion. However, certain differences are noticeable. The heart appears to prefer glucose to lactate. The relationship between blood lactate level and its myocardial extraction is also different from glucose. The extraction of glucose is a function of the logarithm of the arterial concentration; the myocardial lactate extraction plotted against the arterial lactate level follows a parabolic curve (Fig. 9). In general, however, the results from studies of myocardial lactate extraction and usage confirm the conclusions obtained on the heart lung preparation that lactate can be utilized by the myocardium (3-5, 9, 19); these results

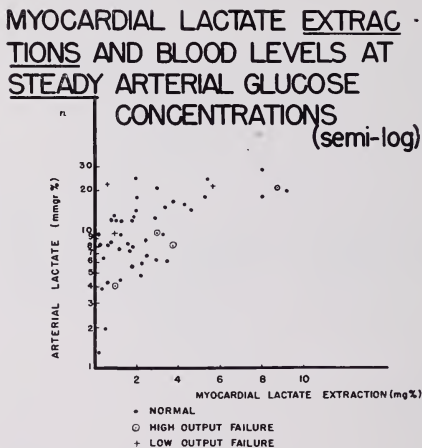


FIG. 9. The relationship of the myocardial lactate extraction plotted against the logarithm of the arterial lactate concentration follows a parabolic curve.

contrast with those obtained in skeletal muscle wherein lactic acid formation represents a dead end of the metabolic pathway..

Pyruvic acid holds a key position in the intermediary metabolism of carbohydrate, participating in both the anaerobic and the aerobic cycles (33). The concentration of pyruvate in blood, however, is extremely low, indicating that, at least under ordinary circumstances, it is rapidly utilized. Because of the small coronary arteriovenous pyruvate differences obtained, no definite conclusions can be drawn on the relationship between arterial pyruvate concentrations and its myocardial extraction and usage. There is little doubt, however, that pyruvate is metabolized by the heart as was first suggested by Braun-Menendez and by others (34, 19). Miller and Olson have recently found that in heart muscle slices the utilization of pyruvate is a function of the initial concentration

of substrate and that the rate of decline in the utilization of pyruvate is a logarithmic function of time (13).

We now turn our attention to the myocardial metabolism of non-carbohydrate substances. It is apparent that in the majority of patients, the total aerobic metabolism of glucose, lactate, and pyruvate combined still falls far short of the total oxygen consumption of the heart (Fig. 10). This is the case even in some patients with high arterial glucose concentration. This suggests that the myocardial oxygen consumption may be covered by aerobic catabolism of non-car-

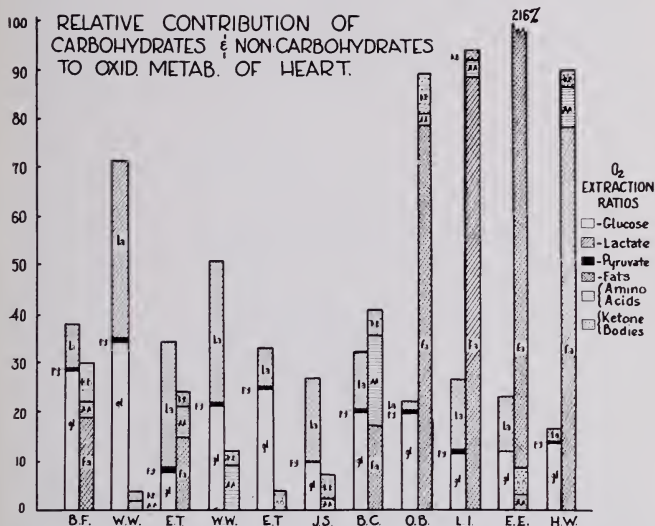


FIG. 10. Contribution of the aerobic metabolism of carbohydrates and non-carbohydrates to myocardial oxygen extraction. In many instances fat appears to be the preferred fuel of the heart muscle.

bohydrate substances. Actually, this is not surprising if it is recalled from animal experiments that carbohydrates are not the essential fuel of muscular contraction and that the necessary energy can be provided from other foodstuffs (14, 35). Thus, activity in the skeletal muscle continues in the depancreatized dog supported by energy derived primarily from fat (33). Fat may be used for storage in the heart muscle cell or it may be burned in the Krebs cycle and used for energy production. It is also apparent that proteins and carbohydrates can contribute to fat storage and that these 2 foodstuffs are closely inter-related with the metabolism of fat (Fig. 11). With our methods, we determine only the

difference in the content of fatty acids between the coronary arterial and venous blood; this gives us no information as to what goes on in the heart muscle cell. However, we know from the work of Schoenheimer, Rittenberg and Stetten that the turnover of depot fat is continuous, that the low saturated fatty acids appear to be consumed more rapidly, and that, as starvation progresses, the unsaturated acids become more and more segregated (36, 37). Peters has recently stated that, in the continuing metabolism, fat has achieved a novel position of importance (30). It is equally an intermediary compound in the metabolism of carbohydrate and the metabolism of carbohydrate and fats cannot be longer separated. He is of the opinion that after an overnight fast, three-fifths of the energy production is sustained by fat. If this were not so, the glycogen stored would be entirely exhausted. When there is no continuous supply of exogenous carbohydrate, the endogenous supply is used with increasing economy as it becomes depleted.

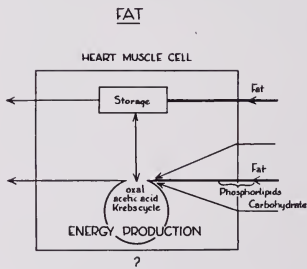


FIG. 11. Possible metabolic pathways of fat in heart muscle cells.

It is not surprising, therefore, that fats are utilized by the human heart muscle (Fig. 10). Work with the heart lung preparation has already pointed in this direction. Bayliss et al, for instance, found very low R.Q.'s of the heart before additions of glucose or insulin (38). Barnes and his co-workers found that as much as 80 % of the total metabolism of the heart can be at the expense of something other than carbohydrate (39). Cruickshank, also utilizing the heart lung preparation, was of the opinion that cardiac fat is replenished from blood fatty acids and that while the heart can and does utilize its store of fat, the primary source of its energy insofar as it is derived from fat, is the blood fatty acid (40). He emphasizes, however, that the utilization of fat by the heart may not be a usual physiological process, since fat utilization has only been demonstrated in the presence of an acute shortage of carbohydrate. Our results seem to indicate that low blood carbohydrate levels are not essential for utilization of fat by the human heart. Of all non-carbohydrate sources, fat contributes the largest amount of energy to the oxidative metabolism of the heart; much in excess of ketone bodies or amino acids. However, there appears to be some relationship between

carbohydrate and non-carbohydrate utilization for oxidative processes, since the oxygen extraction ratio of non-carbohydrate sources by the heart varies inversely with the oxygen extraction ratio of carbohydrates (Fig. 12).

The metabolism of ketones is closely related to that of the 3 main foodstuffs. It has been shown by Waters and associates that in the heart-lung preparation, carbohydrates inhibit ketone utilization and these observations are in accord with the theory of substrate competition for available oxygen (41, 42). Barnes and his group noticed an increase in the utilization of ketones with lowered blood sugar in the heart lung preparation (39). Our data on total ketone body utiliza-

RELATION OF MYOCARDIAL OXYGEN EXTRACTION RATIO OF C.H. AND NON-C.H.

Non-carbohydrate O_2 Extraction Ratio

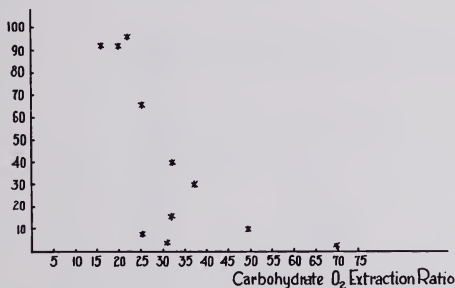


FIG. 12. Relationship of myocardial carbohydrates and non-carbohydrate oxygen extraction ratios. It may be seen that an inverse relationship exists. When the contribution of the aerobic metabolism of carbohydrates to the oxygen extraction of the heart is high, that of non-carbohydrates is low.

tion were collected in individuals in whom no effort was made to either raise or lower the arterial glucose concentrations. At blood ketone levels ranging from 2 to 5 mg. %, the contribution of ketone bodies to the total cardiac oxidative metabolism accounts only for from 3 to 5 % (Fig. 10). It is very likely indeed that during severe starvation or in diabetic acidosis, ketone bodies take over some of the energy and operative producing functions of the heart. Barnes and his co-workers found that in the heart lung preparation 22 % of the total oxygen consumption of the heart could be accounted for by loss of ketone bodies. Their largest contribution to the myocardial metabolism occurred at blood ketone concentrations of over 50 mg. % (39).

We found to our surprise that the human heart is in negative amino acid

balance. Among other things, amino acids may be deaminated and then used for energy production in the Krebs cycle or certain amino acids can be converted to glycogen (Fig. 13). The role played by transamination in muscle is not fully

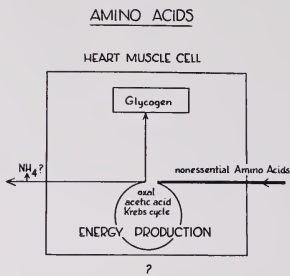


FIG. 13. Possible metabolic pathways of non-essential amino acids in heart muscle.

ARTERIAL GLUCOSE RANGE BETWEEN 110 AND 146 mg %

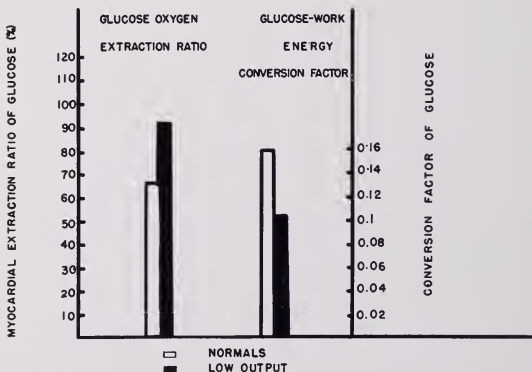


FIG. 14. Comparison of the glucose oxygen extraction ratio and the glucose conversion factor in individuals without failure and in patients with low output failure. The average glucose extraction ratio in failure is increased; the average glucose energy conversion factor is diminished.

understood. Regardless of what happens to the amino acids in heart muscle, the fact remains that their concentration in coronary vein blood is less than that in coronary artery blood.

A few words must be said about our findings on the metabolism of the heart in failure. Thus far, we have information on carbohydrate metabolism only. Results obtained from studies on glucose metabolism of the heart in low and high output failure reveal the same general trend. In the majority of patients in low and high output failure, the myocardial glucose extraction and the glucose oxygen extraction ratios are elevated, and the glucose conversion factor is diminished (Fig. 14a). In high output failure, the myocardial lactate extraction and oxygen extraction ratios are also above values observed in individuals with non-failing hearts. This results in a lowering of the lactate energy conversion factor (Fig.

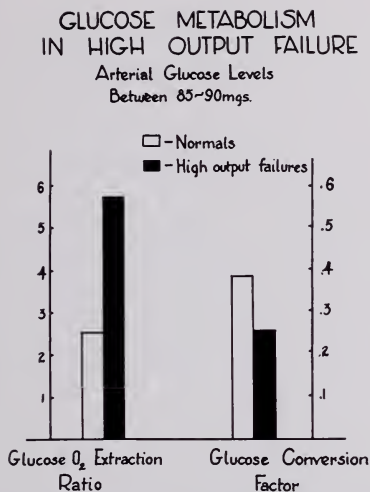


FIG. 14a. In high output failure as in low output failure, there is an increase in the glucose oxygen extraction ratios and the glucose energy conversion factor.

15). As pointed out at the beginning of this lecture, the failing human heart in vivo seems to have partially lost its ability to convert aerobic energy into useful work. The findings on glucose and lactate energy conversion, suggest that the hyper- and hypokinetic heart in failure has also become deficient in converting the energy derived from the aerobic breakdown of glucose and lactate into mechanical work. It is not yet possible to explain the factors which are responsible for the interruption of the link between chemical energy derived from the breakdown of certain metabolites and the work of the heart. On the basis of work on heart muscle proteins which we have recently published, it appears possible that we deal in failure with actual structural physical-chemical changes in the

contractile proteins in actomyosin of heart muscle (43). If this be the case, then the metabolic alterations observed in cardiac failure are only the manifestation and not the underlying cause of the process which lead to failure.

So far, our results have indicated the ability of the heart to utilize all 3 food-stuffs, carbohydrates, fats, and proteins. It also has confirmed data from studies on the heart lung preparation which suggest that the heart muscle utilizes lactate. This illustrates a great versatility of the myocardium in choosing its fuel supply. Alexander and Wiggers in a recent editorial in *Circulation Research* mentioned factors of safety of the heart; among them the ability of cardiac muscle to respond

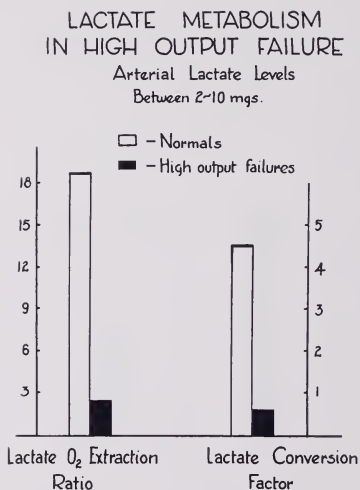


FIG. 15. Comparison of the lactate oxygen extraction ratio and the lactate conversion factor in individuals without failure and in patients with high output failure.

with increased liberation of energy to increased degrees of diastolic stretch, the existence of neural and humoral mechanisms capable of inducing great accelerations in the rate of heart beat, the dilatatory response of the coronary circulation to greatly increased blood flow during anoxemia, the potential contractile force of the atria, and the morphologic property of heart muscle to exhibit hypertrophy (44). Alexander and Wiggers suggest in addition that there may be biochemical factors of safety. One of the most important of these is the ability of the heart to choose its fuel supply from a great variety of foodstuffs. This makes the heart independent of fluctuations in the chemical environment of the body. The heart must therefore possess enzyme systems which enable it to use a great

variety of substrates for energy production and operative function. According to modern concepts of metabolism, these foodstuffs are not handled separately by the heart. It is more likely that in the heart muscle, as in the rest of the body, there is not only kinetic stability but also a dynamic steady state (45). For instance, glucose may be stored in the form of glycogen from which free energy may be available if the necessity arises (kinetic stability). At the same time there is no reason to exempt the heart muscle from the fate of other body tissues in which it has been shown that all components undergo continuous turnover in balance (dynamic steady state).

BIBLIOGRAPHY

1. CRUICKSHANK, E. W. H. AND STARTUP, C. W.: The Effect of Insulin on the Respiratory Quotient, Oxygen Consumption, Sugar Utilization and Glycogen Synthesis in the Normal Mammalian Heart in Hyper- and Hypoglycemia. *J. Physiol.*, 77: 365, 1933.
2. PATTERSON, S. W., AND STARLING, E. H.: The Carbohydrate Metabolism of the Isolated Heart Lung Preparation. *J. Physiol.*, 47: 137, 1913-14.
3. EVANS, C. L., GRANDE, F., AND HSU, F. Y.: The Glucose and Lactate Consumption of the Dog's Heart. *Quart. J. Exper. Physiol.*, 24: 347, 1934-35.
4. EVANS, C. L.: The Metabolism of Cardiac Muscle. *Recent Advances in Physiology*. Sixth edition. Philadelphia, Blakiston, 1939.
5. MCGINTY, D. A.: Studies on Coronary Circulation; Absorption of Lactic Acid by Heart Muscle. *Am. J. Physiol.*, 98: 244, 1931.
6. BOGUE, J. Y., EVANS, C. L., GRANDE, F., AND HSU, F. Y.: Effect of Adrenaline and of Increased Work on Carbohydrate Metabolism of Mammalian Heart. *Quart. J. Exper. Physiol.*, 25: 228, 1935.
7. CRUICKSHANK, E. W. H. AND MCCLURE, G. S.: On the Question of the Utilization of Amino Acids and Fat by the Mammalian Heart. *J. Physiol.*, 86: 1, 1936.
8. CLARK, A. J., GADDIE, R., AND STEWART, C. P.: The Metabolism of the Isolated Heart of the Frog. *J. Physiol.*, 72: 443, 1931.
9. RUHL, A.: Über die Bedeutung der Milchsäure für den Herzstoffwechsel. *Klin. Wchnschr.*, 13: 1529, 1934.
10. STARLING, E. H. AND EVANS, C. L.: The Respiratory Exchanges of the Heart in the Diabetic Animal. *J. Physiol.*, 49: 67, 1914.
11. CLARK, A. J., GADDIE, R., AND STEWART, C. P.: The Carbohydrate Metabolism of the Isolated Heart of the Frog. *J. Physiol.*, 75: 311, 1932.
12. OLSON, R. E. AND SCHWARTZ, W. B.: Myocardial Metabolism in Congestive Heart Failure. *Medicine*, 30: 21, 1951.
13. MILLER, O. N. AND OLSON, R. E.: Metabolism of Cardiac Muscle. IV. Utilization of Pyruvate and DL-Lactate by Duck Heart. *J. Biol. Chem.*, 199: 457, 1952.
14. RICHARDSON, H. B., SHORR, E., AND LOEBEL, R. O.: Tissue Metabolism; Respiratory Quotient of Normal and Diabetic Tissue. *J. Biol. Chem.*, 86: 551, 1930.
15. BING, R. J., VANDAM, L. D., GREGOIRE, F., HANDELSMAN, J. C., GOODALE, W. T., AND ECKENHOFF, J. E.: Catheterization of the Coronary Sinus and Middle Cardiac Vein in Man. *Proc. Soc. Exper. Biol. & Med.*, 66: 239, 1947.
16. BING, R. J., HAMMOND, M. M., HANDELSMAN, J. C., POWERS, S. R., SPENCER, F. C., ECKENHOFF, J. E., GOODALE, W. T., HAFKENSCHIEL, J. M., AND KETY, S. S.: The Measurement of Coronary Blood Flow, Oxygen Consumption, and Efficiency of the Left Ventricle in Man. *Am. Heart J.*, 38: 1, 1949.
17. BING, R. J.: Coronary Circulation in Health and Disease as Studied by Coronary Sinus Catheterization. *Bull. New York Acad. Med.*, 27: 407, 1951.

18. BING, R. J. AND DALEY, R.: Behavior of the Myocardium in Health and Disease as Studied by Coronary Sinus Catheterization. *Am. J. Med.*, 10: 711, 1951.
19. GOODALE, W. T., OLSON, R. E., AND HACKEL, D. B.: Myocardial Glucose, Lactate and Pyruvate Metabolism of Normal and Failing Hearts Studied by Coronary Sinus Catheterization in Man. *Federation Proc.*, 9: 49, 1950.
20. HAGEDORN, H. C. AND JENSEN, B. N.: Zur Mikrobestimmung des Blutzuckers mittels Ferrieyanid. *Biochem. Zeit.*, 135: 46, 1923.
21. SOMOGYI, M.: A Method for the Preparation of Blood Filtrate for the Determination of Sugar. *J. Biol. Chem.*, 86: 655, 1930.
22. FRIEDEMANN, T. E. AND HAUGEN, G. E.: Pyruvic Acid; II. The Determination of Keto Acids in Blood and Urine. *J. Biol. Chem.*, 147: 415, 1943.
23. BARKER, S. B. AND SUMMERSON, W. H.: Colorimetric Determination of Lactic Acid in Biological Material. *J. Biol. Chem.*, 138: 535, 1941.
24. VAN SLYKE, D. D. AND NEILL, J. M.: The Determination of Gases in Blood and Other Solutions by Vacuum Extractions and Manometric Measurement. *J. Biol. Chem.*, 61: 523, 1924.
25. MAN, E. B. AND GILDEA, E. F.: Modification of Stoddard and Drury Titrimetric Method for Determination of Fatty Acids in Blood Serum. *J. Biol. Chem.*, 99: 43, 1933.
26. ALBANESE, A. AND IRBY, V.: The Determination of Amino Nitrogen of Blood Filtrates by the Copper Method. *J. Lab. and Clin. Med.*, 30: 718-21, 1945.
27. GREENBERG, L. A. AND LESTER, D.: A Micro Method for Determination of Acetone and Ketone Bodies. *J. Biol. Chem.*, 154: 177-90, 1944.
28. CORI, G. I., CORI, C. F., AND SCHMIDT, G.: The Role of Glucose-1-phosphate in the Formation of Blood Sugar and Synthesis of Glycogen in the Liver. *J. Biol. Chem.*, 129: 629, 1939.
29. SOSKIN, S. AND LEVINE, R.: Carbohydrate Metabolism. Chicago. The University of Chicago Press, 1946. 315 pp.
30. PETERS, J. P.: Inter-relationships of Foodstuffs. *Ann. New York Acad. Sci.*, 56: 127, 1952.
31. BUTSCH, W. C.: Glucose Tolerance and Glycogen Storage Capacity of the Dog. *Am. J. Physiol.*, 108: 639, 1934.
32. HIMWICH, H. E., KOSKOFF, Y. D., AND NAHUM, L. H.: Changes in Lactic Acid and Glucose in the Blood on its Passage Through Organs. *Am. J. Physiol.*, 85: 379, 1928.
33. PETERS, J. P. AND VAN SLYKE, D. D.: Quantitative Clinical Chemistry. Volume I. second edition. Baltimore, Williams and Wilkins, 1946, 1041 pp.
34. BRAUN-MENENDEZ, E., CHUTE, A. L., AND GREGORY, R. A.: Usage of Pyruvic Acid by Dog's Heart. *Quart. J. Exper. Physiol.*, 29: 91, 1939.
35. HAARMANN, W. AND SCHROEDER, E.: Über die Umwandlung von Fett in Zucker. *Biochem. Ztschr.*, 296: 35, 1938.
36. SCHOENHEIMER, R. AND RITTENBERG, D.: The Dynamic State of Body Constituents. Harvard University Monograph in Medicine and Public Health. Harvard University, 1942.
37. STETTEN, DEW. AND GRALL, G.: Rate of Replacement of Depot and Liver Fatty Acids in Mice. *J. Biol. Chem.*, 148: 509-15, 1943.
38. BAYLISS, L. E., MUELLER, A., AND STARLING, E. H.: The Action of Insulin and Sugar on the Respiratory Quotient and Metabolism of the Heart Lung Preparation. *J. Physiol.*, 65: 33, 1928.
39. BARNES, R. H., MACKAY, E. M., MOE, G. K., AND VISSCHER, M. B.: The Utilization of Beta-hydroxybutyric Acid by the Isolated Mammalian Heart and Lungs. *Am. J. Physiol.*, 123: 272, 1938.
40. CRICKSHANK, E. W. H. AND KOSTERLITZ, H. W.: The Utilization of Fat by the Aglycemic Mammalian Heart. *J. Physiol.*, 99: 208, 1941.

41. WATERS, E. T., FLETCHER, J. P., AND MIRSKY, I. A.: The Relation Between Carbohydrate and Beta-hydroxybutyric Acid Utilization by the Heart Lung Preparation. *Am. J. Physiol.*, 122: 542, 1938.
42. KREBS, H. A.: Untersuchungen uber den Stoffwechsel der Aminosauern im Tierkorper. *Ztschr. f. physiol. Chem.*, 217: 191, 1933.
43. TAESCHLER, M. AND BING, R. J.: Some Properties of Contractile Proteins of the Heart as Studied on the Extracted Heart Muscle Preparation. *Circulation Research*, 1: 129, 1953.
44. ALEXANDER, R. S. AND WIGGERS, C. J.: Editorial, Cardiac Factors of Safety. *Circulation Research*, 1: 99, 1953.
45. STETTEN, DEW., JR.: Thermodynamic, Kinetic and Biologic Stability. *Am. J. Med.*, 8: 251, 1952.

ATHEROSCLEROSIS: A PROBLEM IN NEWER PUBLIC HEALTH*†

ANCEL KEYS

Director, Laboratory of Physiological Hygiene, University of Minnesota

The first part of the title of this paper may be a misnomer. There is no guarantee that the main points of this discussion are actually about arteriosclerosis or the particular variety labelled atherosclerosis. Since the pathological condition cannot be precisely evaluated in life, and is all too seldom verified at death, it is proper to leave the pathologist in command of his own field and to stay within the limits of the facts on which this discussion actually depends; these are the facts seen, recorded, and measured by the clinician, the biochemist and the vital statistician.

The facts to be discussed here concern three sets of items: 1) The first is the broad category of heart disease, or diseases, diagnosed by the clinician as angina pectoris, coronary heart disease, myocardial infarction, chronic myocarditis, and myocardial degeneration. In hospital and vital statistics it is rarely possible to differentiate these clearly so it is convenient to group them, for the present purpose, as "degenerative heart disease." Moreover, there is more than a suspicion that they all, in fact, share some common factors in basic etiology, but details would be out of place here. 2) The second set of items concerns serum cholesterol and allied substances which are currently considered to be importantly related to the development of some, at least, of these conditions in man. The relationship is presumably through the atherosclerotic process but this assumption is not central for my argument. 3) Finally, there is the relationship of the diet to the concentration of cholesterol and allied substances in the serum and to the death rate of the adult population.

Why these have anything to do with public health, even a "newer public health," requires a little consideration. For many decades the official as well as the general view of the subject of "public health" has been that it should be concentrated on a few major questions obviously requiring organized attention beyond the scope of the individual practice of medicine—public sanitation, control of epidemics and infective diseases, record-keeping of mortality and communities health status, and the correction of health hazards where many people congregate, as in schools and factories. These limited horizons are now being extended in two ways. First, there is general public insistence that efforts on a broad front should be made to prevent or decrease the incidence of *all* forms of illness and disability, not merely those that are infective or occupational in origin. Second,

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there is the realization that progress in both prevention and medical care demands increased knowledge which can only come from research. This means research workers and facilities whose contribution is to the common good and whose financial support must come, somehow, from the community. This justifies the fact that a large part of all our medical research is now being supported by the U. S. Public Health Service.

Now on purely financial grounds public health activities, including research, cannot be expanded indefinitely, particularly when we have such a staggering cost for military defense. But the need for major public health attention is clear whenever two conditions exist: First, when there are large numbers of the population suffering disability and death from diseases against which private medical practice is making little headway. And, second, when there is any reason to hope that the incidence of these diseases may be altered by measures applicable to the general population, even if these measures are not yet known.

Degenerative heart disease fulfills these conditions. It is unnecessary to cite the mournful facts about the great numbers of persons, and by no means merely the aged, who are affected. And everyone must admit that the present practice and progress of diagnostic and therapeutic medicine is not solving the problem; the proof is only too clear in our vital statistics. It is possible to argue about the detailed accuracy of death certification and to point out the changing age structure of the population, but no matter what qualifications and refinements of analysis are applied, the general fact remains the same. In the past thirty years, which is as far as acceptable records extend, the age-specific death rate from degenerative heart disease is certainly not decreasing. For males under 70 years, in fact, it is difficult to deny that there has been a steady upward trend. This is particularly striking in view of the fact that the total age-specific death rate, from all other causes, is steadily falling.

The mere existence of an undesirable state of affairs is not, in itself, enough reason to demand a major effort to correct it. There must also be some reason to believe that improvement is possible. In the past, a defeatist attitude about heart disease, particularly degenerative heart disease, has been a major hindrance to effort and even to careful consideration. But it is now abundantly clear that degenerative heart disease is not an inevitable consequence of ageing, beginning in youth and progressing with the years, indifferent alike to medical efforts and improvements in living conditions.

VITAL STATISTICS

The fact that the present high death rate from degenerative heart disease in the United States is not inevitable is easily shown by comparison with some other countries. The objection may be raised that certification of specific causes of death is not very reliable and that different criteria may be applied in different countries. The fact that official vital statistics indicate for Italy, for example, only a small fraction of our death rate from coronary disease conceivably may be explained in this way. But this objection loses much force if death rates for the total of all diseases of the circulatory system are compared. Physicians

may differ in the designation of kinds of heart disease but there is much less doubt when it comes to deciding whether they have to do with heart disease in general.

The data in Table 1 cover the age range from 40 through 64 years, probably the most significant 25 years of life in regard to degenerative heart disease. They show higher death rates from the total of all causes in the United States than in Italy and this disadvantage is more marked when deaths from infective and parasitic diseases and from all forms of violence are excluded. The high death rate from violence in the United States is more than offset by the high death rate from tuberculosis in Italy. When comparison is limited to deaths from all forms of cardiovascular disease, the U. S. rates are far worse than those for Italy. Finally, if only degenerative heart disease is considered, the difference is tremendous. It will be noticed, also, that the U. S. males fare much worse than the U. S. females in these comparisons. This is significant in view of the fact that the incidence of degenerative heart disease in American men is much higher than in American women, particularly before old age.

TABLE 1.

Death rates in Italy (1948) as percentages of corresponding rates in the U.S.A. (1949) for men (M) and women (F) in three age groups for:

1) all causes, 2) all causes less infective and parasitic diseases and violence, 3) diseases of the circulatory system (Category VII in the International list), 4) degenerative heart disease (1).

AGE Sex..	40-44		50-54		60-64	
	M	F	M	F	M	F
1. All causes.....	91	100	77	88	75	97
2. Excl. infective, violence.....	79	87	70	83	73	95
3. Circulatory system.....	35	79	31	59	28	67
4. Degenerative heart.....	20	56	23	48	25	56

The example of Italy is cited because other evidence from Italy, to be presented later in this paper, is particularly relevant to the problem. But Italy is not a peculiar exception. Many other countries appear to have much less degenerative heart disease than in the United States. They certainly have lower total death rates, as shown in Table 2. It may come as a shock to realize that, actually, the mortality record of adults in the United States is poorer than in other comparable countries in the Western World. Most of our inferiority shown in Table 2 is explicable as a result of an excessive amount of degenerative heart disease in this country.

The list in Table 2 includes the countries with good vital statistics which are reasonably comparable in race, climate, culture, medical services and vital statistics. The omissions are Western Germany and Finland, because of major population shifts and other effects from the war, and Iceland, Luxembourg and some colonies and semi-independent states with very small populations. Only poverty-stricken Portugal seems to be an exception to the rule that men in other Western countries have lower mortality rates than in the United States. But

Portugal's bad record is mainly explained by tuberculosis and Table 3 shows a different picture when deaths from infective diseases and violence are excluded.

Detailed study of the vital statistics of all these countries indicates that the differences compared to the U. S., in total age-specific death rates could be largely

TABLE 2

Death rates, from all causes, in 16 countries with a total population of about 220 millions

All values are for the period 1947-1949 and are expressed as percentages of the rates in the United States in 1949.

AGE	40-44		50-54		60-64	
Sex.	M	F	M	F	M	F
Australia.....	75	91	87	96	94	94
Belgium.....	96	89	91	96	97	101
Canada.....	78	91	76	92	84	96
Denmark.....	59	83	63	88	70	100
England & Wales.....	68	78	76	83	93	88
France.....	96	100	91	91	93	91
Ireland.....	80	78	57	86	69	88
Italy.....	91	100	77	88	75	97
Netherlands.....	52	69	56	76	63	89
New Zealand.....	55	72	66	81	85	88
Norway.....	64	78	53	65	54	68
Portugal.....	139	125	99	96	99	103
Scotland.....	93	97	93	100	97	107
South Africa.....	93	108	102	115	94	104
Sweden.....	61	86	63	85	68	92
Switzerland.....	78	97	78	97	88	108
Mean.....	79.9	90.1	76.8	89.7	82.7	94.6

TABLE 3

Death rates, per 1000, among men of three age groups in Portugal (1950) and in the United States (1949)

Lines 1 and 2 give the rates from all causes of death except infective and parasitic diseases and violence. Lines 3 and 4 give the death rates from all diseases of the circulatory system (Category VII in the International Long List or items 24 and 25 in the Abridged List).

AGES	40-44	50-54	60-64
1. Portugal.....	4.2	9.0	23.3
2. U. S. A.....	3.8	11.0	26.0
3. Portugal.....	0.9	1.8	5.2
4. U. S. A.....	1.8	5.9	13.9

or wholly explained by differences in the death rates from degenerative heart disease—coronary heart disease, angina pectoris, chronic myocarditis, and myocardial degeneration.

What is possible for the Italians, and the Norwegians, and the Canadians, and so on, should be possible for Americans. The data in Table 2 are a challenge.

SOME BASIC FACTS

But now let us review a few outstanding facts that bear on the question of the incidence of degenerative heart disease. These will point the way to one promising line of attack on a series of problems ranging from the question of the recognition of the tendency to degenerative heart disease in populations to the development of a physiological hygiene aimed at prevention:

1) It is a fact that, compared with healthy persons of the same age, patients with definite angina pectoris or who have survived a myocardial infarction tend to have blood serum characterized by high cholesterol and certain lipoprotein concentrations, a high cholesterol-phospholipid ratio, and a larger proportion of the total cholesterol in the beta lipoprotein fraction.

2) It is a fact that, on the average, persons afflicted with diabetes, myxedema and nephrosis tend to have high cholesterol and the other serum peculiarities mentioned above. Among these patients there is a high incidence of atherosclerosis and degenerative heart disease.

3) It is a fact that in animal experiments those measures, such as high cholesterol diets and thyroid suppression, which produce high levels of cholesterol and allied substances in the serum, are also productive of atherosclerosis.

4) It is a fact that a major characteristic of the atherosclerotic artery is the presence of abnormal amounts of cholesterol in that artery. The atherosclerotic plaque consists of 40 to 70 per cent cholesterol. It is extremely probable that most or all of this cholesterol is derived from the blood. The cholesterol in the blood does not exist as a simple solution of free and ester cholesterol; it is carried in lipo-protein complexes.

DIAGNOSIS AND PROGNOSIS FROM BLOOD ANALYSIS

All of this indicates that measurement of cholesterol and allied substances in the blood serum affords an indication of the tendency towards the development of atherosclerosis and degenerative heart disease. But two questions arise at once. How reliable is the indication derived from such measurements? And is one or the other of the various measurements much superior to the others for the recognition or prediction of degenerative heart disease in man?

In one sense the reliability is high. Whenever *groups* of individuals are compared, all of these measurements invariably seem to show statistically significant correlations between the measurements and the presence or absence of the tendency towards degenerative heart disease. But the correlations are far from perfect and the reliability is low for single individuals. These statements about the high reliability with groups and low reliability for individuals apply to all of the measurements so far studied: total cholesterol, cholesterol/phospholipid ratio, "giant molecules" of the S_f 10-20 and S_f 12-20 varieties, beta lipoproteins, the fraction of cholesterol in the beta lipoproteins, and so on. Two of the items—total cholesterol and "giant molecules"—have been studied most and merit more detailed consideration. With regard to coronary disease in man these two measurements tend to show parallel tendencies. Experiments with animals can be devised in which this parallelism is disturbed but it is questionable whether

the bizarre situation of the alloxan diabetic rabbit fed enormous amounts of cholesterol (2) has any counterpart in man.

Two years ago, total cholesterol and the S_f 10-20 fraction in the serum were compared (3, 4). It was concluded, from suitable mathematical analysis, that there was then no evidence for an important difference between S_f 10-20 and cholesterol measurements as devices to differentiate between clinically healthy people and patients with definite coronary disease and that neither measure was acceptably reliable in dealing with individuals. More recent evidence tends to confirm the propriety of these conclusions.

Jones and co-workers (2) have presented new data, this time on the S_f 12-20 fraction, and have argued for its superiority to total cholesterol measurement from comparisons made on 550 men, including 156 men who had survived myocardial infarction. The analysis of the data shows, actually, that there was no statistically significant difference between the S_f 12-20 and the cholesterol measurements in the discrimination between "normals" and "infarcts" in the 331 men from 41 to 50 years of age, though, if we accept certain assumptions, in the 219 men from 51 to 60 years of age the S_f 12-20 measurement may have achieved somewhat better discrimination.

The computation made by Jones *et al* (2) assumes that the relationship is rectilinear, that is when the S_f 12-20 or the cholesterol level is doubled the degree of association with infarction also tends to be doubled and so on up and down the scale. There is no evidence that this assumption is proper and the computations of biserial correlation coefficients may, therefore, be invalid.

But, for the moment, let us accept the assumption and ask how good is the computed discrimination. The most favorable results obtained with the S_f 12-20 measurement were with the younger men where a biserial correlation coefficient of $r = 0.62 \pm 0.07$ obtained between the presence of infarction and the concentration of S_f 12-20 in the serum. Jones *et al* (2) argue that the relationship would be even closer with ideally perfect methods and that the correlation they found is "attenuated" by errors in measurement. However, we are concerned about what to expect with the actual methods at hand and this is indicated from the actual correlation coefficient of 0.62. What does this mean in terms of predicting which bloods come from clinically healthy men? This is readily answered in terms of the index of forecasting efficiency. Table 4 summarizes data on the forecasting efficiency in this regard.

The index of forecasting efficiency shows the percentage by which it is possible to reduce the error that would prevail if we tried to predict in the absence of any correlation. The correlation coefficient of 0.62 means an index of forecasting efficiency of about 21 per cent. Consider 1000 men, half of whom are clinically healthy, the others being victims of myocardial infarction. Merely given a list of 1000 code names and the information that half of these pertain to men with infarcts, the effort to classify them would be purely random guesswork and the result would be 500 correct diagnoses and 500 errors. But if S_f 12-20 measurements were made the result could be improved by making 21 per cent fewer errors; one could hope for only 395 errors instead of 500.

It is illuminating to apply this to a more realistic situation as in the last column of Table 4. Take the problem of diagnosing the trend toward infarction before the infarction occurs or the likelihood that a given individual is specifically threatened. If one out of 10 persons presenting themselves for test is actually so threatened and if such threatened persons are really identical in regard to blood chemistry with the men who have had infarcts, the likelihood of deciding which is which, and therefore of being able to give the right advice, would be one chance in ten by sheer random guesswork. With the aid of the S_f 12-20 measurement with men aged 41 to 50 years, the diagnostician's judgement would be improved by 21 per cent; he would make 21 per cent less than 9 errors out of 10. This is almost exactly the same result as would be expected with total cholesterol measurements from the data of Gertler *et al* (5, 6) in men under 50, but Jones *et al* (2) are a little less successful with cholesterol. It should be observed that Jones

TABLE 4

Discrimination between healthy men and patients with coronary disease (infarcts) by ultracentrifugal and total cholesterol measurements

"r" = biserial correlation coefficient; "Index" = index of forecasting efficiency; relative value (Rel. Val.) indicates the chance of assigning a correct diagnosis to a man with coronary disease in a population in which it is known that 10 per cent of the men have coronary disease. Data in lines 2 and 7 from Keys (3, 4) after Gertler *et al.* (5, 6) and Gofman *et al.* (7); lines 3-6 from Jones *et al.* (2).

ITEM	r	INDEX	REL. VAL.
1. No test or measurement.....	0	0	0.10
2. S_f 10-20, 31-50 yrs.	0.41	9	0.18
3. S_f 12-20, 41-50 yrs.	0.62	21	0.29
4. S_f 12-20, 51-60 yrs.	0.61	21	0.29
5. Cholesterol, 41-50 yrs.....	0.46	12	0.21
6. Cholesterol, 51-60 yrs.....	0.30	5	0.15
7. Cholesterol, 31-50 yrs.	0.61	21	0.29
8. Ideal test.....	1.00	100	1.00

et al (2) report far better results with the S_f 12-20 measurement than were obtained by Gofman *et al* (7) with the S_f 10-20 measurement (3, 4).

It seems probable that something like this disappointing situation will continue to be the case with all of the items of blood analysis now proposed or which may be proposed to indicate the development of atherosclerosis and the danger of coronary disease and infarction. How could it be otherwise? A single sample of blood represents only a particular moment but the pathological process is the resultant of the operations of the blood factor (or factors) over many months, years or decades, plus all the other factors which may be concerned—the individual's peculiarities of blood flow, arterial wall and other factors yet unknown.

But this great limitation for individual clinical application should not prevent recognition of the fact that statistically, dealing with groups of people, the measurement of any and all of the items—total cholesterol, giant molecules, etc.—is of great significance. Correlation coefficients of the order of 0.6 do not justify

attempts at individual diagnosis or prognosis but they have high predictive significance for groups, even quite small groups. In about 95 out of 100 samples of only 10 coronary patients the average measurement would be higher than the average for clinically healthy men (Table 4, lines 3, 4, 7). Other things being equal, there seems to be no doubt that high serum levels of cholesterol, etc., are undesirable and the higher the values the more undesirable they are. Hence there is every justification for devoting great effort to discovering what determines the level in man and how that level may be controlled.

CHOLESTEROL IN THE DIET AND IN THE BLOOD

Because of the limitations of both space and data the remainder of this discussion is restricted to the total cholesterol concentration in the blood serum. The serum cholesterol level is the resultant of several factors. All animals, including man, synthesize cholesterol, mainly in the liver, and eliminate it in the bile and by chemical degradation. If there is cholesterol in the food it may be absorbed and so enter the balance picture. But when exogenous cholesterol is supplied the synthesis in the liver is suppressed (8, 9, 10). Some animals, such as the rabbit and the chicken, have little or no dietary experience with cholesterol after weaning or hatching and have little capacity to destroy or otherwise eliminate it when they are fed large amounts. Others, like the rat, the dog and man, have much greater ability to handle cholesterol and are relatively unaffected by dietary administration.

The attempt to extrapolate to man the findings from cholesterol experiments with rabbits and chickens can lead to absurdities. The typical rabbit experiment involves a diet containing 2 per cent added cholesterol, or some 5 mg. of cholesterol per Calorie. This means 15 grams of cholesterol in a human diet of 3000 Calories, an amount about ten times higher than it is *possible* to attain in any habitual diet of ordinary human foods and fifteen or twenty times what is considered a high-cholesterol diet for man (11). And it must be emphasized again that man is very different from the rabbit and the chicken in his metabolism of cholesterol.

In man and animals only a portion of orally ingested cholesterol is absorbed. From experiments with C^{14} labelled cholesterol in the rat (12) and H^3 labelled cholesterol in man (13) it seems probable that something like 20 to 50 per cent of cholesterol ingested in a fat vehicle is absorbed from the gut. But such absorbed cholesterol does not simply add to the cholesterol already present in the blood and the total concentration in the blood rises very little, even with massive doses.

From 20 experiments with young men ingesting 5 to 12 grams of cholesterol in a fat-rich meal it was found the maximum rise in the blood concentration occurred from 3 to 10 hours later but the value at 4 hours was at or near the peak. In Table 5 are the summarized data from experiments on 73 clinically healthy men who were given a breakfast of toast and butter and coffee with cream and scrambled eggs in which 10 grams of pure cholesterol were emulsified. The mean rise of 3.95 mg. per 100 ml. of serum corresponds to an increase of about 250

mg. in the total circulating blood or less than 3 per cent of the ingested cholesterol. Moreover, in 18 to 30 hours the serum level no longer shows any trace of such a single massive dose.

Continued feeding of man with diets containing 20 or more grams of added cholesterol daily eventually produces a rise in the serum level of elderly men (14), but this is trivial compared with the change in rabbits or chickens fed an equivalent amount. The data summarized in Table 6 show how greatly man differs from other animal species, particularly the rabbit and the chicken. It will also be observed that man on an ordinary diet has a higher concentration of cholesterol in the serum than the other animals listed as well as other animals studied on normal diets; these include the cat, cow, goat, guinea pig, horse, and mouse.

Horlick and Havel (19) observed that the maximum effect of dietary cholesterol in the rat is achieved by diets containing around 3 mg. of cholesterol per Calorie and that further increasing this massive dose to heroic proportions has no effect on the blood. The data suggest this may be true of man also. In any case, the

TABLE 5

Means and standard deviations for serum total cholesterol concentrations, in mg. per 100 ml., in 73 healthy young men before and 4 hours after ingestion of 10.7 grams of cholesterol in a fat-rich breakfast

	MEAN	S.D.
Before ingestion	216.35	±36.22
Change after ingestion.....	+3.95	±11.09

problem is not what may be the result of tremendous doses over limited time so much as the effect of prolonged ingestion of far more moderate amounts.

In the United States different persons have greatly different habits in regard to dietary cholesterol. Some persons never drink milk, eat eggs or consume more than minute amounts of butter, ice cream, cheese or fat meat. Others, however, regularly consume several eggs a day and use large amounts of meat and dairy products. The range encountered in a population sample may be from less than 100 mg. to as much as 1 gm. of cholesterol in the daily diet. But extensive surveys of the serum cholesterol concentration in individuals of differing cholesterol intake consistently fail to show a relation between these variables.

Our surveys on clinically healthy men of the upper economic bracket in the Twin Cities have covered several hundred men in each of five successive years. Each year we have obtained negative results similar to those reported for the first year (25) and confirmed by others (6, 26). Perhaps the most significant findings are those obtained on men persistently extreme in their dietary cholesterol habits and on men who changed their dietary cholesterol intakes. Table 7 gives a summary of the data on 63 middle-aged men who were persistently extreme in their dietary cholesterol habits when studied over a period of two years. It is clear that the men who were always above the 80th percentile in dietary chole-

terol did not, at any time, have higher serum values than the men who were always below the 20th percentile of intake.

Table 7 also gives a summary of the data on 40 men who made marked changes in their dietary cholesterol intakes, in some cases because of altered domestic status, in others in a conscious effort to change the cholesterol intake. Primarily, these men changed their dietary habits with regard to eggs and changed from

TABLE 6

Mean serum cholesterol responses to cholesterol feeding in different species

The dietary cholesterol values are rough approximations to enable them all to be expressed on the same scale of mg. of cholesterol per dietary Calorie. References (referring to line numbers) are: 1, 10, 11—Cook and Thomson (15); 2, 3—Kesten and Silbowitz (16); 4, 5—Rodbard, Bolene and Katz (17); 6—Stamler and Katz (18); 7, 8—Horlick and Harvel (19); 9—Sperry and Stoyanoff (20); 12—Greenberg and Rinehart (21); 13—Moses (22); 14—Steiner (23); 15, 16, 17—Messinger, Porowska and Steele (14); 18—Okey and Stewart (24).

SPECIES	DIET MG./CAL.	DURATION, WEEKS	MG. PER 10 ML.		%
			Control	Final	
1. Rabbit.....	5.0	8	149	1720	+1050
2. Rabbit.....	0.6	16	(145)*	430*	+200
3. Rabbit.....	1.5	5-8	141*	959*	+580
4. Chick.....	0.8	25	(100)	130	+30
5. Chick.....	6.0	15	(100)	550	+450
6. Chick.....	0.8	5-15	116	169	+46
7. Rat.....	15.0	22	(59)*	113*	+108
8. Rat.....	30.0	22	(54)*	129*	+139
9. Rat.....	3.0	?	59	163	+176
10. Rat.....	5.0	4	70	222	+217
11. Guinea Pig.....	5.0	5	96	271	+182
12. Monkey.....	3.0	29	175	213	+22
13. Man.....	1.0	16	222	223	0
14. Man.....	1.5	6	—	—	"slight"
15. Man.....	1.3†	7	235	272	+16
16. Man.....	1.3†	6	253	287	+13
17. Man.....	12.0	9+	238	276	+16
18. Man.....	1.4	4	154	167	+8

* Whole blood.

† Cholesterol in dried egg yolk, powder fed. This powder also provided about 20 gm. of lecithin.

butter and lard to vegetable fats, or vice versa. The result was large change in cholesterol intake with little or no change in calories, in total proteins or in total fats and the body weights were practically constant. Here again, as in the surveys of men on constant diets, there was no trace of an effect on the serum concentration of total cholesterol.

In the course of this work it was possible to study 17 men who, though clinically well, changed to a low-cholesterol diet with moderate restriction of all fats. Most of these men were following the advice of their personal physicians who advocated

low-cholesterol diets and fat restriction for all middle-aged men. Prior to the diet change the mean and standard error of the serum total cholesterol concentration was 242.2 ± 14.0 . After 3 to 7 months on the restricted diet the values were 229.9 ± 9.9 . Though this difference is not statistically very impressive, it was important in the design of the systematic experiments to be mentioned below.

TABLE 7

Means and standard errors for serum total cholesterol, in mg. per 100 ml., in clinically healthy middle-aged men, matched as to age, with habitually different cholesterol intakes

The dietary intakes are indicated by the percentile ranks of the men in the total sample of 300 men of the upper economic bracket in the Twin Cities.

NO. MEN	FIRST YEAR		SECOND YEAR*	
	Intake Percentile	Serum Conc.	Intake Percentile	Serum Conc.
35	90	244.7 ± 5.9	90	246.0 ± 6.7
51	10	240.6 ± 8.8	10	244.0 ± 10.3
23	60	250.1 ± 7.1	25	250.3 ± 6.7
17	45	259.7 ± 8.3	70	252.5 ± 10.2

* Corrected for increased age from data of Keys et al. (30).

DIET AND SERUM CHOLESTEROL-CONTROLLED EXPERIMENTS

Like others (27, 28) we had consistently observed a marked decrease in the serum cholesterol concentration in hypertensive patients when treated by subsistence on the rice fruit diet (29). Studies were then made on 21 normotensive men before and during one month's subsistence on a modified rice-fruit diet in which salt was allowed as well as the substitution of potatoes for some of the rice. The results are summarized in Table 8. This diet, containing no cholesterol and extremely little fat—about 1 to 1.5 per cent of the total calories—immediately initiates a decline in serum cholesterol so that in 3 weeks the average is about 70 per cent of the value on an ordinary free diet (30).

More prolonged experiments were carried out on physically healthy schizophrenic men in an isolated metabolism building at the Hastings (Minnesota) State Hospital. In the first series of experiments 21 men were studied in collaboration with Dr. J. T. Anderson, for eight months of alternations of a month each on six diets of constant calorie, protein, mineral and vitamin content but differing in cholesterol and in total fat content. The basic diet was a modified rice-fruit diet, similar to that mentioned above but containing also some egg whites, fat-free bread and boiled green vegetables, to which were added vegetable fats or sugar and jelly to keep calories constant. The cholesterol was added in the form of egg yolks, the fat content of these substituting for an equivalent amount of vegetable fat. The men proceeded through these alternations in different order so possible cumulative effects of particular diet sequences were eliminated in the average serum changes shown in Table 9.

Table 9 clearly shows a pronounced effect of dietary (vegetable) fat and no significant effect of cholesterol in the range 0 to 650 mg. per day. Comparison

of the serum cholesterol values in the third and in the fourth weeks on each diet disclosed no significant difference, indicating that the diet effect was substantially completed in 3 weeks. Concordant results in studies on 3 men have been reported by Hildreth et al (32).

Further evidence on these questions was obtained in an experiment of 32 weeks' duration on 26 schizophrenic men similar to those mentioned above (31). The men, ranging from 27 to 46 years old, were paired off in 2 groups matched as to age, relative body weight, mental diagnosis and habitual physical activity. Two diets were devised, both providing 3400 Calories, 110 gm. of pro-

TABLE 8

Serum total cholesterol concentration, in mg. per 100 ml., before and after 3 weeks of subsistence on a modified rice-fruit diet

Mean values in 21 normotensive men, aged 22 to 45, grouped according to the control serum concentration, the last group including several men with marked idiopathic hypercholesterolemia.

NO. OF MEN	BEFORE	AFTER	CHANGE IN %
7	200	160	20
7	239	160	33
7	417	252	35
21	285.3	190.7	29.3

TABLE 9

Mean changes in serum total cholesterol concentration, in mg. per 100 ml., in 21 men after subsistence for 4 weeks on controlled diets

CHOL. MG./DAY	FAT, GM. DAILY			ALL EXPTS.
	15	72	114	
0	-64	-27	0	-46
600	-61	-21	0	-41
All Expts.....	-63	-24	0	—

teins and 700 mg. of cholesterol but in one (high fat) there were 140 gm. of fat and in the other (moderate fat) there were 70 gm. of fats. In both diets the fats were 90 per cent from animal and 10 per cent from vegetable sources. One group changed from the high to the moderate fat diet and in 4 weeks there was a mean decrease of 21 mg. of cholesterol per 100 ml. of serum. The other group made the reverse dietary change and the result was a mean increase of 27 mg. of cholesterol per 100 ml. of serum. Continued subsistence on these controlled diets for 32 weeks caused no significant further change in the serum and the difference between the serum cholesterol values on the two diets was maintained.

In all of the studies mentioned above the subjects, like the general population of the United States, had lived all their lives to the time of study on diets rela-

tively high in both total fats and cholesterol, and the experimental findings refer only to relatively short periods of change from this life-long pattern. In order to discover relationships with grossly different life-long diets studies were made on clinically healthy men in other countries.

The standard of comparison for such studies are the results on 1492 clinically healthy men in Minnesota as summarized in Table 10 (33). These standards are also valid, apparently, for other metropolitan areas in the United States (34).

The age trend, most clearly shown in the columns of percentages in Table 10, is striking and suggests the age trend commonly observed in the incidence of coronary artery disease. In the following comparisons with men in other countries this age trend is of particular interest.

TABLE 10

"Normal" values for the total cholesterol concentration, in mg. per 100 ml. of serum, for clinically healthy men in Minnesota

The data refer to 1492 men gainfully occupied in non-manual work in the metropolitan area of Minneapolis and St. Paul. Means and standard deviations (S.D.), and means expressed as percentages of the mean at age 25. These values refer to measurements using the Liebermann-Burchard reaction with the Bloor extract of bloods drawn in the basal state; for causal blood samples the values should be increased by about 5 per cent. With the Sperry-Schoenheimer method the values should be about 5 per cent lower, (33).

AGE	MEAN S. D.	%	AGE	MEAN S. D.	%
20	173 ± 31	94	50	248 ± 45	135
25	184 ± 34	100	55	256 ± 46	139
30	195 ± 40	106	60	253 ± 34	137
35	200 ± 43	109	65	237 ± 34	129
40	219 ± 39	119	70	225 ± 42	122
45	236 ± 37	128	75	212 ± 37	115

SERUM CHOLESTEROL VALUES IN OTHER COUNTRIES

In comparison with the United States the diet in Great Britain is interesting. The average fat consumption in Britain is high, though not so high as in the United States (about 11 per cent lower in Britain) and the pattern was not importantly changed during World War II and subsequent years. But the average cholesterol intake is much lower as indicated by the fact that the per capita consumption of eggs, meat and milk, as percentages of that in the United States, is, respectively, 52, 68, and 74 (from National Food Balance Data for 1949-50, supplied by the Nutrition Division, Food and Agriculture Organization of the United Nations).

In the spring of 1950 it was possible to study 48 clinically healthy men employed in Slough, a suburb of London, and these 40 to 55 year-old men, together with the sample of 44 healthy younger men studied in London a few months previously (35) are compared with the Minnesota men in Table 11.

These Englishmen, then, conform closely to the Minnesota standards but this does not mean that the English and American populations are identical in these

respects. The men studied in London are not a true sample because, for one thing, their fat intake was somewhat higher than the national average. A careful study made by the Ministry of Health of food actually eaten by the men at Slough gave an average of 35.4 per cent of calories from fats. Since fat wastage is necessarily considerable between retail purchase and actual consumption, the retail average for these men might correspond to something like 38 per cent of calories from fats, as compared with a national average for Britain of 34.8. For comparison, the retail average for Minneapolis in the winter of 1948 was 41.1 per cent of total calories as fats (data supplied from the U. S. Department of Agri-

TABLE 11

Serum total cholesterol values in clinically healthy men in the London area

Means, in mg. per 100 ml., adjusted to basal conditions, together with percentages of the means at age 25 in England and of the means for equal ages in Minnesota.

AGE	MEAN	% OF VALUE OF	
		Age 25	Minnesota
20	178	96	103
30	193	104	99
40	228	123	104
50	238	129	101

TABLE 12

Serum total cholesterol values in clinically healthy men in Naples

Means, in mg. per 100 ml., adjusted to basal conditions, together with percentages of the means at age 25 and of the means for equal ages in Minnesota.

AGE	MEAN	% OF VALUE OF	
		Age 25	Minnesota
20	176	93	102
30	204	107	105
40	219	115	100
50	218	115	88

culture by Dr. Esther F. Phipard), the intake value being perhaps 36 to 38 per cent.

The important point about the data from England is that, with similar total fat intakes, the serum cholesterol values are also closely similar to those in Minnesota. But the cholesterol intake of these Englishmen was not much more than half that of the Minnesota men, owing to the strict rationing, since 1940, of eggs, butter and meats; margarine and cooking fats are abundant in Britain.

In Naples, Italy, similar studies were carried out on 83 clinically healthy men covering the age range 20 to 56 (36). In Naples the diet proved to be identical with the Italian national average for the percentage of total calories supplied by fats—20 per cent—and therefore about half the U. S. (and Minnesota) level. Serum cholesterol data are summarized in Table 12.

The picture is not different from that in the Englishmen through age 30 but thereafter the age trend does not continue as in England or the United States. From age 40 to age 50 in Minnesota there is a mean rise of 29 mg.; in Naples there is a fall of 1 mg. Statistical analysis, moreover, shows these differences to be highly significant.

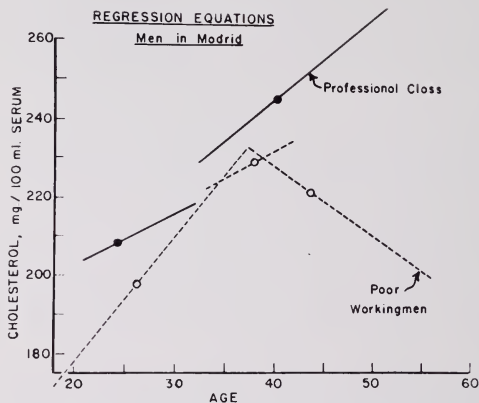


FIG. 1. Relationship of serum total cholesterol concentration to age in clinically healthy Spaniards in Madrid. The lines show the least-squares regression equations for the age ranges covered by these lines, the points being the means for each age series.

TABLE 13

Serum cholesterol values in 2 classes of clinically healthy men in Madrid

Means, in mg. per 100 ml., adjusted to basal conditions, together with percentages of the means at age 25 and of the means for equal ages in Minnesota.

AGE	POOR MEN			RICH MEN		
	Mean	% of Value of		Mean	% of Value of	
		Age 25	Minnesota		Age 25	Minnesota
20	166	91	95	193	98	111
30	199	109	102	201	102	103
40	209	114	95	230	117	105
50	197	105	79	251	127	101

In Madrid, Spain, similar studies were made on 55 poor men habitually always on a low-fat diet (about 22 per cent of calories from fats) and 57 prosperous professional men on a diet similar to that eaten by wealthy men in the United States. The poor men, moreover, were on a low-calorie diet, as indicated both by the dietary survey and by the body weights and measurements of skinfolds. The main findings on these two groups are indicated in Fig. 1.

The prosperous professional men in Madrid are not much different from the Minnesota standards, though they tend to be high at all ages, but they are in great contrast to the poor Madrilenos, especially after 30 years of age. Table 13 summarizes the data from Madrid in a form similar to that used in Tables 11 and 12.

THE FACTOR OF RELATIVE OBESITY

The foregoing analysis emphasizes the role of the total dietary fats in determining the serum cholesterol concentration. The question may be asked, however, as to the role of total calorie balance, particularly in view of the very low serum values in the undernourished poor men in Madrid. However, it seems that relative obesity is not the major factor, short of real undernutrition, when the men in England, in Naples and in Minnesota are considered. The mean relative body weights, as percentage of the Medical-Actuarial standards for height and age used in the United States were as follows: Minnesota 103, Naples 105, England 94. In spite of the relative leanness of the Englishmen, their serum concentrations were not lower than the Minnesotans. And the Neapolitan serum concentrations differ, after age 30, from the Minnesota values in spite of the fact they were a trifle fatter than the Minnesotans.

These facts are in harmony with our findings in Minnesota where we have studied the correlation between serum cholesterol and relative obesity. There is a positive correlation but it is small in men of equal ages in the general population (25). However, chronic severe undernutrition is almost always associated with low serum cholesterol concentrations (34, 37). This may be in part because the fat content of the diet in such cases is always low. We have consistently found increased values in men when they were actively gaining weight from simple overeating. In simple fasting the usual tendency for the serum cholesterol to rise may reflect the fact that the fasting man is primarily metabolizing fat; in a sense then he is on a high-fat diet (34).

THE DIET AND MORTALITY

All the data summarized here suggest an important chain of relations between the total fat content of the diet (or the proportion of fat calories of the total metabolized), the cholesterol (and lipoprotein) concentration in the blood, the development of atherosclerosis, and the mortality from degenerative heart disease. The vital statistics data for Italy (Table 1) clearly fit this pattern.

It is unfortunate that vital statistics data are not available for Spain but perhaps those from Portugal (Table 3) may serve to indicate what may be the case in Spain where the diet is similar. There seems to be no doubt that coronary disease and myocardial infarction are not common in Spain. This is agreed by the local doctors and is confirmed by a search through the public hospitals. But it is also of interest that the leading fashionable physicians do not lack cases among their rich patients and tell of many relatives and colleagues who have died from occlusions.

So far it has been possible to get fully comparable dietary and vital statistics data from 6 countries. Figure 2 gives a summary for men of two age ranges. This

is for "degenerative heart disease" as defined here to mean coronary disease, angina pectoris, infarction, chronic myocarditis and myocardial degeneration, i.e. categories 93 and 94 in the 1938 Revision of the International List and categories 420 and 422 in the 1948 Revision (1). Almost the same relation holds, moreover, if the total deaths from all heart disease are plotted against fat calories as a percentage of the total. This is because of the dominance of these categories in the cardiac total at these ages. Obviously the relation shown in Fig. 2 is too regular and too marked to be explained on the grounds of possible differences between countries in the criteria for death certification. Whether or not chole-

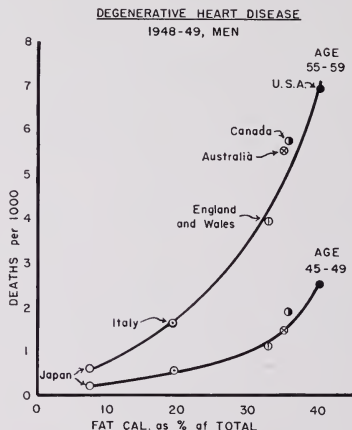


FIG. 2. Mortality from degenerative heart disease (categories 93 and 94 in the Revision of 1938, categories 420 and 422 in the Revision of 1948, International List. National vital statistics from official sources. Fat calories as percentage of total calories calculated from national food balance data for 1949 supplied by the Nutrition Division, Food and Agriculture Organization of the United Nations.

terol, etc., are involved, it must be concluded that dietary fat somehow is associated with cardiac disease mortality, at least in middle age.

There is other impressive evidence to this same effect. World War II brought with it dietary alterations in many areas and a reduction in dietary fat was prominent for several years in lands conquered by Germany. In Norway, the public health and vital statistics records were well maintained and it is clear that not long after the national dietary change began there was a marked decline in mortality from circulatory disease, particularly from arteriosclerotic heart disease (38). At first this change in mortality was attributed to a reduction in dietary cholesterol (39), but detailed analysis indicates that a reduction in total dietary fats was the responsible factor (40).

DISCUSSION

The argument and evidence assembled here make a consistent picture which holds promise of a preventive hygiene but many details are lacking. The mechanism of the action of the diet on the blood cholesterol concentration has not really been examined. This is an important part of the blood cholesterol level (41). We should like to know how, apart from dietary peculiarities, hypercholesterolemia tends to run in families (42, 43, 44). Moreover, there is much reason to believe that other factors besides the blood concentration are important in the actual development of arteriosclerotic heart disease. Why are men and women so different, until well beyond the female reproductive age range, in susceptibility? So far the blood studies have been made mostly on men but at least to age 30 or a little older there seems to be no difference in the blood adequate to account for the sex difference in coronary disease incidence in the United States.

Recognition of all those limitations should not interfere with the analysis of the facts now at hand. It may be hoped that efforts to discover and to understand mechanisms will be pursued vigorously. There is, however, obviously a fruitful

TABLE 14

Fat calories as a percentage of the total calories in the U. S. National food supply since 1910
Computed by Dr. E. Phipard from official data of the U. S. Department of Agriculture.

	%		%		%
1910	31.8	1930	35.0	1950	40.2
1920	33.0	1940	38.3		

field for epidemiological research as yet scarcely touched. And it is not too soon to begin the application, by educational means, of epidemiological findings.

The present high level of fat in the American diet did not always prevail and this fact may not be unrelated to the indication that coronary disease is increasing in this country. Table 14 shows the average fat calories as a percentage of the national food calorie supply from 1910 (the beginning of reliable data) through 1950. In the past 40 years the contribution of fats to the total metabolism in the United States has risen by more than 25 per cent; in the past 20 years the rise has been almost 13 per cent. In the fact of all the evidence, is this situation desirable? One may seriously ask whether the current nutritional and dietetic teaching in this country is as completely on the right track as some may suppose. Complete indifference to the amount of the fat in the diet is the attitude currently expressed by both technical and popular books and articles on diet.

From the statistics of the U.S. Department of Agriculture it is clear that the biggest contributor to the fats in the American diet is fats and oils as such, excluding butter, which comprise 46.5 per cent of the total. Meats, poultry and fish combined make a poor second at 22.1 per cent. Any attempt to reduce the total fat intake must, then, begin with cooking fats and oils.

CONCLUSIONS

The material discussed above covers too large a field to be summarized except in terms of the conclusions which emerge from it. These are:

1) Compared with other countries where records are comparable, the total age-specific death rate over most of the span of adult life is excessively high in the United States and this American inferiority is more marked with men than with women.

2) The excessive death rate of adults in the United States is attributable to an excessive mortality from "degenerative" heart disease—coronary disease, angina pectoris, myocardial infarction, chronic myocarditis and myocardial degeneration. These conditions cannot be clearly separated in vital statistics and probably share some common features in basic etiology.

3) The concentration of total cholesterol in the blood serum bears an important relationship to the development of atherosclerosis and its sequelae and related clinical conditions. Similar relationships exist with the concentrations of certain "giant molecules" (S_f 10-20, S_f 12-20) and of certain lipoprotein fractions separable by precipitation methods.

4) Measurements of total cholesterol and of S_f 12-20 particles in the serum afford highly significant differentiation between *groups* of men who are clinically healthy and *groups* of men who have or are likely to develop coronary heart disease. There is no important difference between the cholesterol and the S_f 12-20 measurements in this regard, particularly with men before old age.

5) These measurements of total cholesterol or of S_f 12-20 concentrations in the serum have very little practical value for individual diagnosis or prognosis, the index of forecasting efficiency being of the order of 20 per cent.

6) The total cholesterol concentration in the serum of man is substantially independent of the dietary cholesterol intake over the whole range of possible human diets.

7) The total cholesterol concentration in the serum of men habitually on diets characteristic of the United States changes directly with changes in the total fat content of the diet. The response to the new diet begins in a few days and reaches a new plateau in a few weeks, this new plateau being relatively stable for at least several months. There is no indication of a difference in animal versus vegetable fat in evoking the serum response.

8) Comparison of men from populations always living on different amounts of total fat intake indicates that in youth and to the early thirties the serum cholesterol concentration is relatively independent of the diet if there is calorie sufficiency. But from the thirties through the fifties the serum concentration is increasingly dependent on the amount of total fat in the diet.

9) The different age-specific death rates of men 40 to 65 years old from degenerative heart disease in different countries are directly related to the differences in those countries in the proportion of the total calories derived from total fats. The relationship in the case of women is much less clear.

10) For the 40 years of records available, the proportion of fat calories in the total American food consumption has steadily increased. On the basis of compari-

sons with other countries at present this rise in fat consumption might be predicted to be associated with an increase of the order of 50 to 100 per cent in mortality from degenerative heart disease for men aged 40 to 65. U. S. vital statistics are, in fact, compatible with this prediction.

11) The facts and relationships indicated here are of such importance as to warrant a large extension of this type of epidemiological research. It is difficult to escape the conclusion that public health programs must take cognizance of the information already at hand.

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REFERENCES

1. World Health Organization. Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death. Sixth Revision of the International Lists of Diseases and Causes of Death, Adopted 1948. Vol. 1. W.H.O., Geneva, 1948.
2. JONES, H. B., GOFMAN, J. W., LINDGREN, F. T., LYON, T. P., GRAHAM, D. M., STRISOWER, B., AND NICHOLS, A. V.: Lipoproteins in Atherosclerosis. *Amer. J. Med.*, 11: 358, 1951.
3. KEYS, A.: "Giant Molecules" and Cholesterol in Relation to Atherosclerosis. *Bull. Johns Hopkins Hosp.*, 88: 473, 1951.
4. KEYS, A.: Cholesterol, "Giant Molecules," and Atherosclerosis. *J. Amer. Med. Assoc.*, 147: 1514, 1951.
5. GERTLER, M. M., GARN, S. M., AND LERMAN, J.: The Interrelationship of Serum Cholesterol, Cholesterol Esters, and Phospholipids in Health and in Coronary Artery Disease. *Circulation*, 2: 205, 1950.
6. GERTLER, M. M., GARN, S. M., AND WHITE, P. D.: Diet, Serum Cholesterol and Coronary Artery Disease. *Circulation*, 2: 696, 1950.
7. GOFMAN, J. W., JONES, H. B., LINDGREN, F. T., LYON, T. P., ELLIOTT, H. A., AND STRISOWER, B.: Blood Lipids and Human Atherosclerosis. *Circulation*, 2: 161, 1950.
8. SCHOENHEIMER, R. AND BREUSCH, F.: Synthesis and Destruction of Cholesterol in the Organism. *J. Biol. Chem.*, 103: 439, 1933.
9. GOULD, R. G.: Lipid Metabolism and Atherosclerosis. *Amer. J. Med.*, 11: 209, 1951.
10. FRANTZ, I. D., JR., SCHNEIDER, H. S., AND HINKELMAN, B. T.: Relationships Between the Levels of Dietary, Liver and Serum Cholesterol and Hepatic Cholesterol Synthesis. *Circulation*, 6: 467, 1952.
11. KEYS, A.: Human Atherosclerosis and the Diet. *Circulation*, 5: 115, 1952.
12. CHAIKOFF, I. L., BLOOM, B., SIPERSTEIN, M. D., KIYASU, J. Y., REINHARDT, W. O.,

- DAUBEN, W. G., AND EASTHAM, J. F.: C^{14} -Cholesterol. 1. Lymphatic Transport of Absorbed Cholesterol-4- C^{14} . *J. Biol. Chem.*, 194: 407, 1952.
13. BIGGS, M. W., KRITCHEVSKY, D., COLMAN, D., GOFMAN, J. W., JONES, H. B., LINDGREN, F. T., HYDE, G., AND LYON, T. P.: Observations on the Fate of Ingested Cholesterol in Man. *Circulation*, 6: 359, 1952.
14. MESSINGER, W. J., POROSOWSKA, Y., AND STEEL, J. M.: Effect of Feeding Egg Yolk and Cholesterol on Serum Cholesterol Levels. *Arch. Internal Med.*, 86: 189, 1950.
15. COOK, R. P. AND THOMSON, R. O.: The Absorption of Fat and of Cholesterol in the Rat, Guinea-pig and Rabbit. *Quart. J. Exp. Physiol.*, 36: 61, 1951.
16. KESTEN, H. D. AND SILBOWITZ, R.: Experimental Atherosclerosis and Soya Lecithin. *Proc. Soc. Exp. Biol. & Med.*, 49: 71, 1942.
17. ROBBARD, S., BOLENE, C., AND KATZ, L. N.: Hypercholesteremia and Atheromatosis in Chicks on a Restricted Diet Containing Cholesterol. *Circulation*, 4: 43, 1951.
18. STAMLER, J. AND KATZ, L. N.: Production of Experimental Cholesterol-induced Atherosclerosis in Chicks with Minimal Hypercholesterolemia and Organ Lipidosis. *Circulation*, 2: 705, 1950.
19. HORLICK, L. AND HAVEL, L.: The Effect of Feeding Propylthiouracil and Cholesterol on the Blood Cholesterol and Arterial Intima in the Rat. *J. Lab. & Clin. Med.*, 33: 1029, 1948.
20. SPERRY, W. M. AND STOYANOFF, V. A.: Effects on Long Continued Cholesterol Feeding in Rats. *J. Nutrition*, 9: 131, 1935.
21. GREENBERG, L. D. AND RINEHART, J. F.: Plasma Cholesterol Levels of Cholesterol Fed Control and Pyridoxine Deficient Monkeys. *Proc. Soc. Exper. Biol. & Med.*, 76: 580, 1951.
22. MOSES, C.: Dietary Cholesterol and Atherosclerosis. *Amer. J. Med. Sci.*, 224: 212, 1952.
23. STEINER, A.: Cholesterol Metabolism and Arteriosclerosis. *Amer. J. Med.*, 6: 117, 1949.
24. OKEY, R. AND STEWART, D.: Diet and Blood Cholesterol in Normal Women. *J. Biol. Chem.*, 99: 717, 1933.
25. KEYS, A.: The Physiology of the Individual as an Approach to a More Quantitative Biology of Man. *Fed. Proc.*, 8: 523, 1949.
26. WILKINSON, C. F., JR., BLECHA, E., AND REIMER, A.: Is There a Relation Between Diet and Blood Cholesterol? *Arch. Int. Med.*, 85: 389, 1950.
27. KEMPNER, W.: Treatment of Hypertensive Vascular Disease with Rice Diet. *Amer. J. Med.*, 4: 545, 1948.
28. SCHWARTZ, W. B. AND MERLIS, J. K.: Nitrogen Balance Studies on Kempner Rice Diet. *J. Clin. Invest.*, 27: 406, 1948.
29. CHAPMAN, C. B., GIBBONS, T., AND HENSCHEL, A.: The Effect of the Rice-Fruit Diet on the Composition of the Body. *New England J. Med.*, 243: 899, 1950.
30. KEYS, A., MICKELSEN, O., MILLER, E. v. O., AND CHAPMAN, C. B.: The Relation in Man Between Cholesterol Levels in the Diet and in the Blood. *Science*, 112: 79, 1950.
31. ANDERSON, J. T. AND KEYS, A.: Dietary Fat and Serum Cholesterol. *Fed. Proc.*, in press.
32. HILDRETH, E. A., MELLINKOFF, S. M., BLAIR, G. W., AND HILDRETH, D. M.: The Effect of Vegetable Fat Ingestion on Human Serum Cholesterol Concentration. *Circulation*, 3: 641, 1951.
33. KEYS, A., MICKELSEN, O., MILLER, E. v. O., HAYES, E. R., AND TODD, R. L.: The Concentration of Cholesterol in the Blood Serum of Normal Man and Its Relation To Age. *J. Clin. Invest.*, 29: 1347, 1950.
34. KEYS, A., BROZEK, J., HENSCHEL, A., MICKELSEN, O., AND TAYLOR, H. L.: The Biology of Human Starvation. 2 Vols: Minnesota Press, Minneapolis, 1950.
35. TANNER, J. M.: The Relation Between Serum Cholesterol and Physique in Healthy Young Men. *J. Physiol.*, 115: 371, 1951.

36. KEYS, A., FIDANZA, F., SCARDI, V., AND BERGAMI, G.: The Trend of Serum Cholesterol Levels with Age. *Lancet*, 263: 209, 1952.
37. HORST, W.: Beitrag zum Lipidstoffwechsel bei Chronischer Unternährung. *Klin. Wschr.*, 28: 184, 1950.
38. STRØM, A. AND JENSEN, A. R.: Mortality from Circulatory Diseases in Norway 1940-45. *Lancet*, 260: 126, 1951.
39. MALMROS, H.: The Relation of Nutrition to Health. A Statistical Study of the War-time on Arteriosclerosis, Cardiosclerosis, Tuberculosis and Diabetes. *Acta Med. Scand. Suppl.*, 245: 137, 1950.
40. PIHL, A.: Cholesterol Studies. II. Dietary Cholesterol and Atherosclerosis. *Scand. J. Clin. and Lab. Invest.*, 4: 122, 1952.
41. BYERS, S. O., FRIEDMAN, M., AND ROSENMAN, R. H.: Review: On the Regulation of Blood Cholesterol. *Metabolism*, 1: 479, 1952.
42. BOAS, E. P. AND ADLERSBERG, D.: Familial Hypercholesteremia (Xanthomatosis) and Atherosclerosis. *J. Mt. Sinai Hosp.*, 12: 84, 1945-1946.
43. WILKINSON, C. F., JR., HAND, E. A., AND FLIEGELMAN, M. T.: Essential Familial Hypercholesteremia. *Ann. Int. Med.*, 29: 676, 1948.
44. ADLERSBERG, D.: Hypercholesteremia with Predisposition to Atherosclerosis. An Inborn Error of Lipid Metabolism. *Amer. J. Med.*, 11: 600, 1952.

METACHRONOUS CARCINOMAS OF THE DUODENUM AND THE COLON*

GERSON J. LESNICK, M.D.

Carcinomas of the duodenum are relatively infrequent. Loggan and Kleinsasser (1) in a recent review of reported pancreatico-duodenal resections for this disease collected 123 cases of which 11 were performed for carcinomas arising in the second or third portion of the duodenum. Of the remaining operations, 38 were performed for carcinomas of the ampulla of Vater, 62 for carcinomas of the head of the pancreas and 12 for a miscellaneous group of malignancies arising in the bile ducts, stomach, pancreatic duct, and ascending colon. Of the 11 patients with neoplasms of the duodenum, 2 died within 3 months of operation, 6 died within 3 months to 2 years following operation, 1 was not followed, and 2 were living 3½ and 4 years following operation.

The case to be presented is of interest in that the patient did well for 21 months after a pancreatico-duodenal resection for a duodenal carcinoma. Fifteen months following the first procedure he developed a second independent carcinoma of the hepatic flexure which was successfully resected. Loggan and Kleinsasser cite one similar case reported by Brunschwig, of a second primary carcinoma of the colon developing in a patient surviving pancreatico-duodenectomy. This was a patient operated upon in 1943 for a carcinoma of the ampulla of Vater. Two and one-half years later he had a right colectomy for carcinoma of the ascending colon and was reported well in July 1950, 7 years after the original resection.

CASE REPORT

J. C. entered the Mount Sinai Hospital on May 11, 1950, with a history of increasing weakness and fatigue for 6 months. For 4 weeks he had noted postprandial epigastric pain, anorexia and weight loss. One week before admission he became icteric. Aside from slight icterus physical examination revealed no abnormality. Laboratory tests disclosed the following: hemoglobin—8.0 gms.; urine—faint trace of bile; stool—4+ guaiac; serum bilirubin—1.0 mg; alkaline phosphatase—40 King Armstrong Units; blood cholesterol—420 mgm. %; esters—270 mgm. %; total protein—5.9 gms. Studies of the duodenal secretions suggested intermittent biliary and pancreatic duct obstruction and demonstrated the presence of blood. A gastro-intestinal x-ray series revealed a deformity of the second portion of the duodenum suggesting a carcinoma (Fig. 1). The barium enema x-ray showed no abnormality (Fig. 2). The icterus subsided under observation.

Operation

On May 29, 1950 the antrum of the stomach, the first and second portions of the duodenum and the head of the pancreas were resected; the distal third portion of the duodenum and the duodeno-jejunal flexure were mobilized; the common duct was implanted into the side of the third portion of the duodenum over a T-tube brought out through a separate choledochostomy incision; the pancreatic duct, which was not dilated, was ligated and the pancreatic stump was closed with interrupted sutures. A gastro-jejunostomy was then

* From the Department of Surgery, The Mount Sinai Hospital, New York, N. Y.

performed about one foot distal to the biliary anastomoses with a drain applied to the stump of the pancreas.

Pathology

The specimen revealed an infiltrating carcinoma of the second portion of the duodenum. There were no involved lymph nodes. The ampulla of Vater was not obstructed and entered the superior lip of the tumor. The distal 1 cm. of the common duct was infiltrated by tumor but not narrowed. The pancreatic duct could not be found.

Course

The patient did well for five days following operation and then developed a pancreatic fistula. This was accompanied by the appearance of an inflammatory mass in the right



FIG. 1. Gastrointestinal x-ray series (May, 1950) showing filling defect in the second portion of the duodenum.

upper abdominal quadrant, paralytic ileus, intestinal obstruction, increasing icterus and a biliary leak. Pancreatic juice drained in quantities reaching as much as 1000 cc. a day. Bits of necrotic pancreatic tissue and necrotic fat were discharged from the wound. Maintenance of fluid balance presented a major problem and forty days after operation, a jejunostomy was performed for alimentation. A large inflammatory mass in the right upper quadrant was seen. The icterus slowly subsided but a secondary anemia, hypoproteinemia with blood total proteins of 4.3 gms. % and anasarca ensued. Fifty-eight days after operation, pancreatic drainage finally became slight and 10 days later he was discharged to a nursing home where he slowly regained his appetite and strength. He was discharged three months later following a gain in weight and the disappearance of edema. He was well for 3 months when increasing weakness appeared. Two months later an anemia with a hemoglobin of 10.0 gms. was found. Stool analysis showed a 4+ guaiac reaction and a

barium enema x-ray examination in June 1951 disclosed a large filling defect at the hepatic flexure (Fig. 3).

He was readmitted to the hospital on July 10, 1951. Physical examination revealed a moderate anemia and well healed scars of the previous operations. There were no palpable abdominal or rectal masses. The hemoglobin was 11.2 gms., and the stool guaiac reaction was again 4+. A barium enema x-ray revealed a large irregular polypoid defect in the hepatic flexure (Fig. 3). Gastrointestinal x-ray series demonstrated a well functioning



FIG. 2. Barium enema x-ray examination (May 1950) showing normal hepatic flexure.

gastro-enterostomy stoma (Fig. 4). In view of the presence of so large a defect without a palpable abdominal mass, a second primary tumor was considered more likely than a local recurrence of the old tumor.

Operation

On July 16, 1951 an operation was performed. The abdominal scar from the previous operation was excised. There were many thin adhesions in the upper abdomen, particularly in the right upper quadrant. The hepatic flexure of the colon was the site of a large mass which was confined primarily to the mucosal and submucosal tissues. At one point the mass had penetrated to the serosa and was adherent to the adjacent portion of the right transverse colon. There was no evidence of extracolonic involvement, nor was there tumor



FIG. 3. Barium enema x-ray examination (July 1951) showing a filling defect in the hepatic flexure.



FIG. 4. Gastrointestinal x-ray series (July 1951) showing the well functioning gastroenterostomy stoma.

in the bed of the earlier pancreatic resection; the liver was free of metastases. The right colon to the mid-transverse area and six inches of the terminal ileum were resected. Intestinal continuity was restored by side to side ileotransverse colostomy.

Pathology

The specimen showed an infiltrating carcinoma of the colon, with no involved lymph nodes. A segment of liver adherent to the tumor was free of disease.

Course

The post-operative course was complicated by an abscess presenting in the drainage tract of the first operation; after this was drained on the 10th day after operation, he did well and was discharged 9 days later.

Two months after the patient was discharged drainage from the fistula had ceased. He was well until April 1952 when abdominal pain, jaundice and fever again appeared. This continued until his death on July 18, 1952. Exploratory laparotomy shortly before death demonstrated recurrence of carcinoma around the common duct.

The pancreatic fistula was the major problem in management. A pancreatico-jejunal anastomosis was not performed because the pancreatic duct was not dilated and so would have presented an almost insurmountable technical problem.

A review of the influence of ligation or anastomosis of the pancreatic duct upon the results of pancreatico-duodenal resection as reported in the literature is of interest. Unfortunately, many of the reports do not give details of the operative procedure; this is especially true of those who died at or after operation. In 80 of 123 reported (1) cases there was a note concerning the disposition of the pancreas. Of 40 cases in which the stump was sewn over, 19 fistulae developed and 8 died. Of 40 cases in which the duct was implanted into the jejunum, 2 developed fistulae and 3 died. This difference in mortality and morbidity is significant and would suggest that in all cases of pancreatico-duodenal resections the pancreatic duct should be anastomosed to the bowel.

SUMMARY

A case is reported in which an independent carcinoma of the ascending colon appeared one year after resection of a carcinoma of the duodenum.

REFERENCE

1. LOGGAN, POWELL B., AND KLEINSASSER, LEROY J.: Surgery of the Pancreas: The Results of Pancreatico-duodenal Resections Reported in the Literature. *Int. Abs. Surg.*, 93: 521, 1951.

BILATERAL TEMPOROMANDIBULAR ANKYLOSIS

REPORT OF A CASE*

LEO STERN, JR., D.D.S., GABRIEL P. SELEY, M.D., AND NORMAN CRANIN, D.D.S.

Ankylosis of the temporomandibular joint is occasionally seen following a comminuted fracture of the condyle, intra-articular hemorrhage, or the extension into the joint of a suppurative process such as an osteomyelitis or middle ear infection. A fibrous type of limitation is more common than bony fusion of the joint. In civilian practice it is fairly unusual to encounter either a false (extra-articular) ankylosis or a bilateral involvement. However, following severe injuries of the face with fracture of the coronoid process of the mandible, zygomatic arch, or lateral wall of the maxilla, particularly if associated with soft tissue infection, fibrous adhesions or bony attachments may form outside the joint and restrict movement of the jaws. The present case is considered unusual in that it includes a bilateral bony fusion of the temporomandibular joints with bony and fibrous limitation of the left coronoid process. A satisfactory restoration of oral function was achieved.

The patient, a poorly nourished Puerto Rican male aged 42, was in an automobile accident 5½ years prior to admission and sustained several injuries including a compound fracture of the humerus and bilateral fractures of the mandible. The jaw injury remained untreated, and two months after discharge from another hospital the patient noticed the onset of trismus. This progressed until six months later when he was unable to open his jaws to the slightest degree. During the ensuing 5 years he subsisted on a liquid and semi-solid diet. This was achieved only by forcibly knocking out his upper incisor teeth. His weight dropped from 165 to 120 pounds. System review elicited a history of occasional abdominal pains with paucity and irregularity of bowel movements which were attributed to the poor diet.

Physical examination was essentially negative except for the complete limitation of opening of the jaws (1-2 millimeters movement), which largely prevented intraoral examination. The vestibule was in an extremely poor state of hygiene and widespread caries of the remaining teeth was present. The face was asymmetrical with a deviation of the midline of the chin to the right (Fig. 1). The temporomandibular joint region on each side displayed a heavy prominence of bone, with the temporal fossa hollowed by atrophy of the temporalis muscle. The ascending rami were shortened and the mandibular angle quite rounded and obtuse.

Roentgenograms (Fig. 2-5) revealed bilateral healed fractures slightly above the angles, with one or two centimeters of overlapping bone. The *right* joint was completely obscured by dense bone. The bony architecture of the ramus also was altered by a thickened cortex and coarse trabeculation. The *left* joint presented a fairly normal appearance, while the coronoid process showed a singular flatten-

* From the Dental and Oral Surgery Service, The Mount Sinai Hospital, New York.



FIG. 1. Preoperative photograph displaying prominence of joint regions, shortened rami, and asymmetry from previous fracture.

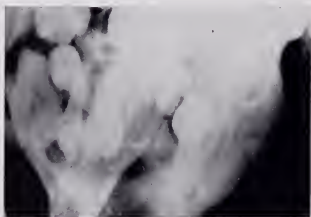


FIG. 2. Right mandible showing massive bony overgrowth of joint and deformed ramus

ing with an oval-shaped window, resembling a doughnut. The interpretation of these findings together with the clinical impressions may be summarized as follows:

a) An exuberant callus formation, indicated by the hard masses bilaterally, prevented both condyles from functioning. The right articulation showed bony ankylosis, while the left probably was involved only by fibrous union.

b) The left coronoid process was split longitudinally by the previous fracture, which healed in the form of a ring with cicatrix binding it intimately to the zygomatic arch and maxilla.

It was decided to perform a condylectomy on the right side in the hope that physiotherapy could overcome the remaining hindrance from scar tissue and



FIG. 3. Right mandible following section above the angle. Space of one centimeter has partly collapsed, but a fibrous joint exists.



FIG. 4. Left mandible with ring-shaped comminuted coronoid process. Joint apparently normal but proved also to be ankylosed.

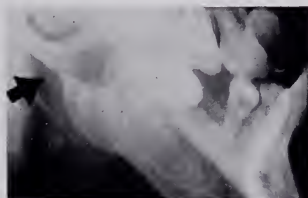


FIG. 5. Left mandible following mid-ramus section and arthroplasty

alleviate the ankylosis of the left joint. The technique of anesthesia administration was exceedingly difficult, requiring blind nasotracheal intubation while the patient was awake. After this was accomplished, the pentothol-ether anesthesia was uneventful. A pre-auricular incision was contemplated, but the massive prominence of bone was too forbidding. Accordingly, the incision was made over the posterior border of the ramus curving around the angle (1). Blunt dissection exposed the body of the ramus and partial retraction of the masseter muscle and

parotid gland permitted palpation of the sigmoid notch. It was felt at this point that a mid-ramus resection was advisable in preference to exposing the deformed condyle with the increased hazard of facial nerve injury. An osteotome was used to sever the ramus and a one centimeter wide section was removed. The edges were rounded with rongeur and file and a flap of masseter muscle sutured into the newly created articulation. The upper half was tested and found to be joined solidly to the skull. The greater part of the mandible now could be moved with

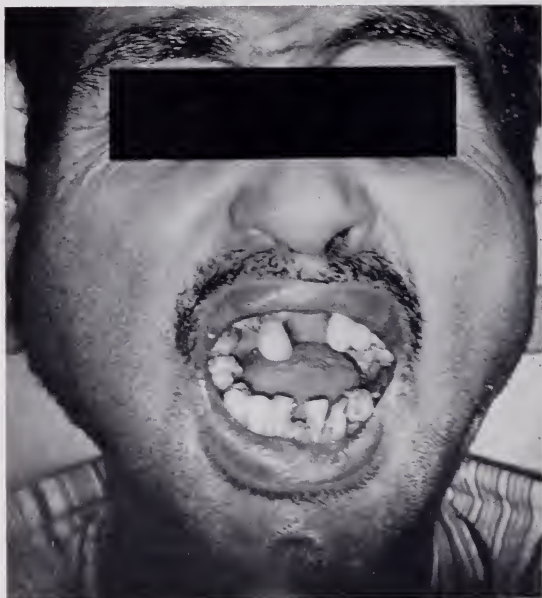


FIG. 6. Degree of opening (24 mm.) following surgical section of both rami

partial freedom, but was still apparently anchored at the other joint. The wound was closed in layers and a small Penrose drain inserted.

After ten days, healing was sufficient to institute diathermy and muscular exercises, with a consequent increase in opening of the mouth to 6 millimeters. No further improvement was noted, so that on the 26th day a left coronoidectomy was attempted on the theory that the coronoid process was responsible for the continued fixation. An incision was made intraorally and a long handled osteome used to section the two separate bony processes. Guide xrays showed the

coronoid to be completely disattached. There was no apparent benefit, however, indicating a probable bony ankylosis of the medial aspect of the condyle. On the 42nd day, therefore, a complete ramus resection was performed on the left side, duplicating the first procedure.

Convalescence was rapid, with an immediate increase of intermaxillary opening to over two centimeters. The movement of the jaw in closing was now like that of a door without a hinge, so that no real biting pressure could be exerted by the anterior teeth. This picture was gradually changed by a collapse of the open segments and fibrous thickening at the new joints. The patient can now chew vigorously and painlessly with both molar and incisor function. The degree of opening measures 24 millimeters (Fig. 6). He achieved a weight gain of 15 pounds in the first three weeks following discharge. The more diseased teeth are now being removed in order to construct prosthetic appliances and complete his rehabilitation.

COMMENT

The surgical correction usually advocated for the relief of ankylosis of the temporomandibular articulation is resection of the condyle. When this operation is confined to one side, the derangement of normal function is minimal. After bilateral condylectomy, however, the relative disability as compared with normal function may be considerable (2). The change in anatomic position and the curtailment of motion may be summarized as follows:

1. Owing to loss of the external pterygoid muscles, the depression of the mandible must be taken over by the reeducated infrahyoid and suprahyoid muscle groups. This opening is of a hinge type, lateral or protrusive movement being impossible.

2. There is a retrusion of the mandible due to loss of the anterior capsular ligament, causing a displaced occlusion to which the patient cannot accommodate. A new centric relation must be fashioned by reshaping or rebuilding the dentition.

3. The lack of condylar support together with scar contraction causes an open anterior bite with premature contact of the molar teeth. Relief by grinding is followed by further collapse as the gap previously occupied by the condyle is gradually closed.

While complete ankylosis may at times justify the restoration of function by any means, these patients frequently require the grinding or removal of posterior teeth to alleviate the premature closure, which is progressive. They remain dental cripples.

In the present case, the situation was altered by the destruction of both dental arches and by the low line of section of the previously shortened rami. As compared with the malunion following the earlier fractures, further retrusion of the mandible was unlikely.

It was anticipated that closure of the lower jaw would solely depend on the masseter muscle and would not involve a fulcrum action as represented by the temporomandibular joint. There was no question of restoring normal occlusion

or ramus height. Also, the resultant scar contraction and shortening of vertical height was not so great as to interfere appreciably with the prosthetic problem. Since the entire occlusion had to be reconstructed, the relative deformity could be compensated.

SUMMARY

A case of severe ankylosis involving both temporomandibular joints and one coronoid process is presented. Complete surgical section and arthroplasty of both mandibular rami were performed, since the condyle and coronoid process could not be freed separately. Despite the fact that only a portion of the masseters remained functional among the elevator group of muscles, the patient was able to develop satisfactory mastication.

REFERENCES

- (1) KAZANJIAN, V. H. A., 2ND, AND CONVERSE, J. M.: *The Surgical Treatment of Facial Injuries*. Baltimore, 1949. The Williams & Wilkins Co., 493.
- (2) SMITH, A. E., AND ROBINSON, W.: Mandibular Function after Condylectomy. *J. Amer. Dental Assn.*, 46: 304, 1953.

REVELATIONS FROM THE EARLY ANNUAL REPORTS OF THE MOUNT SINAI HOSPITAL

JOSEPH HIRSH, ED.D.

In the preparation of the centennial history of the Mount Sinai Hospital*, literally hundreds of reports and documents of all kinds had to be abandoned in the selection process. Almost without exception, these documents contained commentaries of the times and of the early Hospital which have a distinctive place in historical reporting. The early Annual Reports constitute a body of information on those aspects of the Hospital's life which the medically and scientifically minded, more often than not, take for granted. This brief contribution, therefore, based largely upon extracts of these early Annual Reports, reveals certain human aspects of the Hospital not recorded in our centennial history.

Thus in the Report for "the year commencing December 25, 5616 (1855)", the year the Hospital opened its doors to patients, "and ending December 31, 5617 (1856)" 216 patients were admitted, representing a variety of national groups or countries. In this and in subsequent listings it will be noted that many of these "countries" were, in reality, duchies, princedoms, provinces and not countries at all as we know them in the modern sense. Many of them, moreover, are now that part of history which is reflected in the absorption of small countries by larger ones or their integration into new national states.

<i>Natives of</i>		<i>Natives of</i>	
United States.....	5	Bohemia.....	7
England.....	9	Sweden.....	2
France.....	3	Switzerland.....	2
Germany.....	110	Galicia.....	1
Poland.....	64	Hungary.....	1
Holland.....	6	Denmark.....	1
Russia.....	1	Morocco.....	4

In the "tabellae" of the Annual Report for 5624-25 (1864-65), the countries of origin of the patients admitted to the Hospital are even more illustrative of the foregoing point.

<i>Natives of</i>		<i>Natives of</i>	
Austria.....	2	Hesse Cassel.....	8
Baden.....	14	Hesse Darmstadt.....	11
Bavaria.....	34	Holland.....	7
Bohemia.....	6	Holstein.....	2
Braunschweig.....	2	Hungary.....	9
England.....	17	Ireland.....	19
France.....	5	Lippe.....	1
Frankfort.....	2	Mecklenburg.....	2
Hamburgh.....	1	Oldenburg.....	1
Hanover.....	5	Poland.....	99

* Hirsh, J., and Doherty, B.: The First Hundred Years of the Mount Sinai Hospital of New York: 1852-1952. Random House, New York, N. Y., 1952.

<i>Natives of</i>		<i>Natives of</i>	
Prussia.....	43	Sweden.....	1
Russia.....	12	Switzerland.....	2
Saxony.....	4	United States.....	93
Schwarzenburg.....	0	Wurtemberg.....	5
Scotland.....	1		

Of commensurate historical significance are the tables in the early Annual Reports describing the occupations of the patients admitted. Thus, in the first Annual Report, the occupations are listed in the following table. A number of them, it will be noted, are unique as they are characteristic of the period. Even the most casual reader of these Annual Reports will note per the following table the listing of 3 comedians, 1 daguerreotypist, 1 jockey, 1 moel, 1 tassel maker and 2 traders (to be distinguished from merchants).

<i>Occupations</i>	<i>Occupations</i>	<i>Occupations</i>
2 Bakers,	1 Farmer,	1 Paper dealer,
1 Barber,	2 Glove makers,	35 Pedlars,
2 Book binders,	11 Glaziers,	1 Sailor,
2 Book keepers,	23 House keepers,	1 Sexton,
5 Butchers,	1 Jockey,	4 Shoemakers,
3 Cap makers,	1 Laborer,	1 Shopkeeper,
6 Cigar makers,	4 Merchants,	1 Seamstress,
3 Comedians,	1 Moel,	1 Tassel maker,
1 Carpenter,	2 Milliners,	1 Teacher,
10 Clerks,	1 Music teacher,	1 Tinsmith,
1 Cloth dyer,	2 Nurses,	12 Tailors,
2 Cooks,	1 Oil dealer,	1 Tanner,
1 Daguerreotypist,	2 Old men,	2 Traders,
31 Domestics,	2 Painters,	10 Unknown.

The list of occupations in the Annual Report for 1864 is equally instructive. There is a quality of charm when one considers in the following list that childhood is viewed as an occupation—full-time and geographical. The glaziers, alas, in this plastic age, are now a part of history and the *segarmakers* (the spelling in most of the early Annual Reports) have now been replaced by the modern cigarmaker.

Occupation		Occupation		Occupation	
Bakers.....	3	Drivers.....	2	Peddlers.....	47
Barbers.....	3	Druggist.....	1	Physician.....	1
Barkeepers.....	2	Dyer.....	1	Seamen.....	2
Blacksmiths.....	2	Engineer.....	1	Segarmakers.....	22
Bookbinder.....	1	Furriers.....	3	Shoemakers.....	4
Boilermaker.....	1	Glaziers.....	11	Soldiers.....	58
Brewers.....	2	Goldsmiths.....	2	Tailors.....	15
Butchers.....	6	Housekeepers.....	42	Teachers.....	3
Capmakers.....	2	Laborers.....	19	Tinsmith.....	1
Chemist.....	1	Lacemaker.....	1	Upholsterer.....	1
Children.....	27	Merchants.....	15	Weaver.....	1
Clerks.....	23	Musicians.....	3	Washerwomen.....	2
Confectioner.....	1	Nurses.....	3	Watchman.....	1
Domestics.....	53	Painters.....	2		
Dressmakers.....	9	Paperhanger.....	1		

While a hospital is neither bricks nor mortar, neither doctors nor patients nor funds but a sound integration of these and many other factors, money goes a long way to make the Hospital possible. This was as true then as it is now. Compared to the present budget of over \$6,000,000, the following budget for the year 1864 covering less than 1 printed page is most instructive.

Insurance.....	\$145.00
Bread.....	874.82
Milk.....	344.59
Groceries	1,625.31
Beef	1,915.11
Medicines.....	808.62
Surgical Instruments.....	245.56
Salaries.....	1,987.36
Shirts, muslin, drygoods.....	760.38
Glazier, carpenter, plumbing, painting, garden work, house-cleaning, kalsomin- ing sidewalk and repairs.....	234.09
Gas.....	113.61
Delivery of Election Notices	10.00
Coal and wood.....	810.00
Funeral expenses.....	153.50
Tombstones.....	39.00
Making shrouds.....	16.05
Carriage hose	1.50
Newspapers	6.82
Croton Water Taxes.....	170.00
Grave-digging.....	23.00
Dr. Teller—stage fare, postage	14.84
Ice	32.90
Collecting bills of 1864	166.75
Furnace, crockery, hardware, and repairs of same.....	125.38
Stationery and Directory, 1864	40.18
Soap and starch.....	71.64
Garden hose, rope, &c	37.10
Sundries	333.47
	<u>\$11,106.58</u>

Patient care depended not only upon budgets but upon contributions in cash as well as kind. Compared to the contributions made to the modern Hospital, those recorded in the Annual Report for 1871 are instructive as they are charming. Thus in January, the following donations were received:

Barrel of apples and oranges
Clothing
Ice cream to every patient.

In March there were:

100 Charlotte Russe
30 cakes
Wine
4 gallons ice cream
12 brooms
Clothing.

In May:

Twenty dollars
Clothing
Funeral pall
2 pair India-rubber stockings
Easy chair
A bouquet of flowers to every patient.

In October:

Barrel of apples
One hundred and eighty dollars
Pair candlesticks
Clothing
Barrel potatoes
Lint.

This report presents facets from the early life of the Hospital, previously unreported but not overlooked in the wealth of archival material that is extant. It is hoped that this source material, readily available in the Hospital, will be exploited in preparing other contributions to medical history.

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CONTENTS

THE IMPORTANCE OF THE LABORATORY IN ANTIBIOTIC THERAPY. <i>S. Stanley Schneierson, M.D. and Morton S. Bryer, M.D.</i>	155
STUDIES IN MYASTHENIA GRAVIS: EDROPHONIUM CHLORIDE (TENSILON) TEST AS A NEW APPROACH TO MANAGEMENT. <i>Kermit E. Osserman, M.D., Lawrence I. Kaplan, M.D., and Gerald Besson, M.D.</i>	165
THE SIGNIFICANCE OF BILATERAL ABNORMALITY IN THE ELECTRO-ENCEPHALOGRAM. <i>Mortimer Ostow, M.D., Med.Sc.D., and Hans Strauss, M.D.</i>	173
PSYCHOPHYSIOLOGICAL STUDIES OF FISTULOUS OPENINGS INTO THE GASTROINTESTINAL TRACT. <i>Sydney G. Margolin, M.D.</i>	194
PRIMARY CARCINOMA OF THE LUNG. <i>Arthur H. Aufses, M.D.</i>	212
GRANULOSA CELL TUMOR. <i>Alexander Bellwin, M.D. and M. A. Goldberger, M.D., F.A.C.S.</i>	229
BOOK REVIEW	236

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* Deceased

THE IMPORTANCE OF THE LABORATORY IN
ANTIBIOTIC THERAPY*

S. STANLEY SCHNEIERSON AND MORTON S. BRYER

With the advent of antibiotic therapy in the treatment of infectious diseases, the laboratory has become an indispensable adjunct to the rational employment of these chemotherapeutic agents. It can prove of inestimable value to the clinician in many different ways. It can discover the causative agents of the disease process and determine their susceptibility to any available antibiotic, singly or in combination. The progress achieved with the instituted treatment program can best be followed with the aid of the laboratory. If the anticipated clinical results are not forthcoming, determination of the blood or other body fluid concentrations of the drug may furnish a clue to the reasons for this failure by revealing incomplete absorption or excessive excretion of the antimicrobial agent. Since a combined clinical and laboratory approach offers the greatest opportunities, closest liaison should be maintained at all times between both. Without such cooperation therapy is at best hit or miss and the outcome uncertain. Intelligent administration of these valuable medicaments often requires the assistance of a qualified laboratory in order to achieve maximal exploitation of their full potential. Judicious employment of its services can mean the difference between success and failure. This applies to hospital cases particularly, many of whom are admitted after empirically selected home treatment has failed to produce a satisfactory response; in fact many are transferred to the hospital for the sole purpose of enlisting the aid of the institutional laboratory facilities. For this reason hospital cases are more apt to represent difficult therapeutic problems and the laboratory assumes an even greater importance in these cases.

Many mild or uncomplicated illnesses are successfully treated with antibiotics without subjecting patients to the expense, effort and time required for a bacteriological investigation. In acute or fulminating infections, where the patient is often too ill to risk delay, postponement of treatment until the laboratory examinations are complete may only invite disaster. Faced with such a dilemma, the physician has no other alternative than to proceed, basing his selection of antibiotics upon his previous clinical experience or upon recommendations reported in the medical literature. Whenever possible, however, it is of prime importance that he obtain appropriate specimens prior to starting therapy so that if satisfactory responses do not result, changes can be initiated based upon information subsequently provided by the laboratory. Delay is more justifiable in less severe or more stubborn cases, especially those that tend to recur and become chronic. Here, where the need for speed is less imperative, postponement of treatment until the laboratory studies are concluded may be

* From the Department of Microbiology of The Mount Sinai Hospital, New York, N. Y.

condoned as frequently these data are essential for placing treatment on a firmer basis particularly where initial empirical administration of antibiotics has proven fruitless.

Complaints are levelled at the laboratory because of the "excessive" time required for the performance of its procedures. It must be realized that a period of time is needed to accomplish isolation and to complete identification of the etiological agent as well as for the performance of sensitivity tests. The techniques employed are biological in nature and involve the cultivation of microorganisms under artificial conditions. Some of these, e.g. *Mycobacterium tuberculosis* and *Brucella*, require considerable time. Nothing can be done to expedite this, no matter how desirable, since the inherent time requirement for the growth of each strain is beyond technical control. In some instances it may be necessary to resort to animal inoculations and even weeks may supervene before the characteristic diagnostic lesions appear. One is obliged to yield to these limitations even though the time requirements mitigate against the usefulness of the laboratory. However, an extremely valuable, simple and rapid procedure, which is all too often omitted, that can obviate the time difficulty, is the preparation of smears from pathological material. From examination of these smears, unstained, or prepared with special stains such as Gram, Ziehl-Neelsen or examined under the dark-field microscope, sufficient information can often be obtained to make a satisfactory tentative diagnosis in a number of conditions, based upon which an effective therapeutic regime can be formulated. The use of smears for diagnosis is of special value in tuberculosis, in which the growth time requirement is unusually onerous; in leprosy, where it remains the only practical method of diagnosis; in syphilis and gonorrhea; and in infections of the meninges, the urinary tract, the upper respiratory tract, the ear and conjunctivae as well as in surface infections.

DIAGNOSIS

The nature and cause of an infectious disease cannot be determined with certainty without the assistance of appropriate laboratory tests. The correct diagnosis may be suspected with a fair degree of accuracy on the basis of history, epidemiology and the clinical aspects but in atypical cases accurate diagnosis is often impossible without laboratory confirmation. In order to treat properly, it is imperative that the nature of the invading organism be ascertained and only the isolation and identification of the etiological agent provides the physician with an exact diagnostic measure. For example, a wide variety of bacteria can be and are responsible for producing a number of identical clinical conditions. Meningitis is usually caused by any one of the following microorganisms; meningococcus, pneumococcus, streptococcus pyogenes, hemophilus influenzae or parainfluenzae, escherichia coli, and mycobacterium tuberculosis. Likewise in blood stream infections many different bacteria may be isolated, i.e. streptococcus viridans, streptococcus fecalis, staphylococcus aureus and albus, escherichia coli, salmonellae, proteus, pneumococcus and meningococcus, and others. The clinical syndrome produced with each organism may not be characteristic

and may fail to afford any clue as to which species is responsible for any given case. From inspection of the great variety of organisms noted above, it can be readily seen that the antibiotic offering the greatest therapeutic potential for the same clinical condition can differ markedly and that exact identification of the etiological agent is the prime essential for the choice of an effective therapeutic regime. Where such delicate organisms as pneumococcus, gonococcus, meningococcus and most strains of streptococcus hemolyticus are involved, identification alone can be a guide as to which course to pursue since all strains of these species, with but very rare exceptions, have proven universally susceptible to the action of appropriate antibiotics. Therefore, except in unusual circumstances, it is rarely necessary to perform sensitivity tests with these bacteria routinely.

When an organism is isolated in the laboratory, the causal relationship between the isolated microorganism and the disease must be definitely established. Its presence may be transient or insignificant or may be the result of contamination either in the collection of the specimen or during handling in the laboratory. The clinical picture, persistence of the organism in repeated cultures as well as the pathogenic potential of the isolated species should indicate its true role in the infection. If the exact status of the isolated organism is not established unnecessary treatment or even delay in treatment of the real offender may result.

To obtain maximum benefits, close liaison and cooperation should be established between the laboratory and the clinician. Frequent consultation may prove helpful to both. The laboratory can provide important directions as to the best method and the optimal time for collection of specimens as well as recommending the media offering the best conditions for the successful isolation of the causative agent. On the other hand, the laboratory must be fully advised regarding previous administration of growth inhibiting drugs so that it can promptly initiate appropriate measures to neutralize or dilute out the antagonistic effect of these agents in the specimens. This is done in order to increase the chances of recovering the causative bacteria. Pertinent information regarding the history and suspected diagnosis should also be furnished to the laboratory so that special media and animal inoculations may be employed where indicated. Close cooperation in the manner described above undoubtedly results in a significant increase in the percentage of successful isolations and thereby permits the laboratory to be of even greater service to the clinician.

Not infrequently the patient presents himself at a stage in his disease when the etiological agent can no longer be isolated as in the later phases of typhoid fever or syphilis or in the chronic stage of brucellosis. The laboratory, by employing such indirect procedures as agglutination or complement-fixation tests, can often provide the correct diagnosis. These discover and measure immune antibodies produced in the patient during the course of or as a consequence of his infection. In some instances, by means of these procedures, the nature of the problem at hand can be delineated as precisely as if the responsible agents were isolated and identified. A maintained elevated or a rising agglutination titer found on periodic examination of the serum is significant and diagnostic.

SENSITIVITY TESTS

A most important contribution of the laboratory to antibiotic therapy is the determination of the susceptibility of microorganisms involved in an infection to one or more antibiotics, singly or in combination, since as a rule there is no way of distinguishing between sensitive and resistant strains without resort to these tests. As noted above, this may be of little consequence where such universally sensitive organisms as pneumococcus, meningococcus or gonococcus are concerned. However, where hardier species such as *escherichia coli*, staphylococcus, streptococcus fecalis, proteus or pseudomonas aeruginosa are present, the situation may be entirely different and the assays may prove all important. When new antibiotics were introduced, a high proportion, particularly of the first three species mentioned, were found to be relatively susceptible to their action but with the passage of time and their more widespread employment an increasing percentage of strains within these species are proving to be resistant to some of these chemotherapeutic agents. This complication has developed with such rapidity and to so marked a degree with the sulfonamides and with streptomycin that their clinical effectiveness is now greatly circumscribed. So far this has not been true with penicillin, with one exception. Numerous recent reports (1, 2, 3) attest to striking progressive increase in the percentage of penicillin-resistant staphylococci so that the majority of strains now isolated from pathological material are resistant to this antibiotic, many to a marked degree. A number of similar changes with respect to aureomycin and chloramphenicol by a number of different species has also been noted. Thus it has been shown (4) that a greater proportion of strains of *escherichia coli*, proteus, staphylococcus aureus and albus and streptococcus fecalis are now resistant to aureomycin and of *escherichia coli*, proteus and pseudomonas aeruginosa to chloramphenicol as compared to three years ago when the drugs were first introduced to clinical practice. Moreover, in many groups there is a marked variation in the susceptibility of individual members to any particular antibiotic so that generalizations with respect to a given species are no longer tenable. The susceptibility of any given strain can only be determined by the performance of sensitivity tests and the standard tables of sensitivities reported in the literature or distributed by some of the pharmaceutical houses can no longer be relied upon as a guide for the selection of suitable antibiotics. For example, a strain of *escherichia coli* isolated from a patient may range from being very sensitive to markedly resistant to one or all of the following; the sulfonamides, streptomycin, aureomycin, terramycin and chloramphenicol. Without the benefit of sensitivity studies, the clinician may be at a loss as to which antibiotic to prescribe and the patient may be obliged to undergo a series of therapeutic trials with various drugs until the hoped for response is elicited. In addition to the cost and discomfort involved, such a procedure is not without risk since very valuable time may be lost in some instances where early and vigorous treatment is essential to effect a cure.

A serious complication of antibiotic therapy is the problem of residual infections with ordinarily resistant organisms such as proteus or pseudomonas aeruginosa, which are capable of producing severe and even fatal infections.

Their control may require the administration of more active but more toxic drugs like polymyxin or neomycin. Although most infections caused by these organisms are usually resistant to the action of aureomycin, terramycin or chloramphenicol, an occasional one is sensitive and responds to treatment with these less hazardous antibiotics (5, 6). Provision of this vital information by the laboratory may therefore be life saving.

Finally, the performance of sensitivity tests helps build up the experience of the laboratory. By this means evidence is accumulated as to the results that can be anticipated with any particular drug. This can be of considerable value in helping to educate the physician as to what he can expect with any new or established chemotherapeutic preparation. With experience and time the capabilities and limitations of each antimicrobial agent become more clearly delineated.

Clinical results, however, do not always parallel in vitro findings. The laboratory tests merely report the end-results of carefully controlled but artificial conditions many of which are not operative naturally. Moreover, many intrinsic factors present in the body also greatly influence clinical results and these cannot be measured by laboratory determinations. The concentration of antibiotic at the site of infection, the number of infecting organisms at this focus as well as the nature of the lesion with its effect upon the extent and degree of inflammatory reaction are all of importance. The organisms may be deep-seated and surrounded by fibrous and granulation tissue and may thus be protected from the action of the antibiotic. In addition, the type and extent of the reaction to the invasion markedly influences the ability of the antimicrobial drug to penetrate into the focus. Another important determinant is the immune response of the host to the bacterial infection. In pneumonia this may be of paramount importance since all that is ordinarily required to control such infections is to keep the pathogens in check until the immune mechanism elicited in this disease can come into play to overcome the invasion. By contrast, the immune response to streptococcus viridans in subacute bacterial endocarditis is almost negligible and before a cure can be realized the bacteria buried deep in the vegetations on the heart valves must be completely destroyed. Mere inhibition of growth without eradication usually results in recurrence and failure. In spite of the factors noted above, none of which are measured during the performance of sensitivity tests, a surprising degree of correlation is found between the in vitro assays and the clinical response in a significant percentage of cases. Thus the finding of a markedly resistant etiological agent in the laboratory almost always precludes the chances of achieving a gratifying therapeutic result. On the other hand, if the causative organisms have been found to be sensitive in vitro success is more apt to follow provided the natural factors noted above are taken into consideration.

The method of determining bacterial sensitivity routinely employed in this laboratory is the "tube dilution" method. It is reliable, relatively accurate and the results are readily reproducible provided all factors involved in its performance such as the type of medium used, its pH, the size of the inoculum and the temperature and length of incubation are all carefully standardized (7).

Although laborious and expensive in time, materials and effort and requiring the services of specially trained technicians, the detailed and precise information which it provides makes it very worthwhile. The test is performed by adding an amount of a standardized inoculum of the organism tested to a series of tubes containing different concentrations of antibiotic. After appropriate incubation the endpoint is read by noting the first tube, containing the least amount of antibiotic, in which multiplication of the test organism has been inhibited as indicated by visual absence of growth. A parallel determination is made with a standard organism selected for its sensitivity, as a basis for comparison. The exact point of inhibition can be closely measured by means of this procedure and when this amount is equated with the concentration required to inhibit the standard sensitive bacterium under identical cultural conditions, the result can be expressed as a numerical index of resistance. This offers a more precise definition of the status of the organism being examined than the general descriptive terms of "Sensitive" or "Resistant". Generally, when the organism under investigation is found to be less than ten times as resistant as the standard it can be considered as being sensitive; eleven to twenty times as moderately sensitive; above this as resistant; and over one hundred times as markedly resistant. As routinely employed only the bacteriostatic or inhibitory endpoint is determined but the procedure can be easily modified to ascertain the bactericidal or lethal concentration for the bacteria in question. Technically, this is accomplished by the addition of an antibiotic antagonist to the clear tubes where no visible growth has occurred in order to neutralize the growth-inhibitory effect of the antimicrobial drug and then subculturing these tubes to determine at what point no organisms have survived. Where no specific antagonist is available, the contents of each tube can be inoculated into large volumes of culture medium thereby diluting the antibiotic in each tube beyond its growth inhibitory concentration. The subcultures are sterile when all the organisms are destroyed.

The bacteriostatic activity of an antibacterial substance, as discussed above and as measured by the "tube dilution" technique provides the clinician with the minimal concentration of antibiotic that he must secure at the site of infection in order to obtain a cure in most diseases. The growth inhibiting action is usually sufficient where a good blood supply plus the host resistance factors normally present in the natural history of the disease can combine to successfully eliminate the invading organisms. However, where these mechanisms do not operate, in subacute bacterial endocarditis for example, an empirical blood level of five to ten times the minimal inhibitory concentration is usually sought. A more accurate goal might be provided in this disease by the bactericidal endpoint where it is believed that a minimum requirement for the successful treatment of this condition is the constant maintenance of antibiotic levels in excess of bactericidal concentration. In general, at the levels usually obtainable in the body, the effect of penicillin, streptomycin, bacitracin, neomycin, polymyxin and erythromycin is bactericidal while bacteriostasis is more common with the sulfonamides, aureomycin, terramycin and chloramphenicol.

Another very important advantage of the tube dilution method is that it lends

itself readily to the determination of the effect of combinations of chemotherapeutic agents upon any given strain of bacteria. There are many valid reasons for administering more than one antibiotic at a time. The infection with which one is dealing may be caused by a mixture of organisms, each in turn being sensitive to different drugs. The use of two agents may prevent or delay the emergence of bacterial resistance as illustrated in the use of paraminosalicylic acid with streptomycin in the treatment of tuberculosis. Where one or both drugs are potentially toxic and if the same effect can be produced with smaller doses of each component combined, reactions may be minimized by administering two antibiotics at a time using smaller doses of each. The most compelling indication for using some combinations is the fact that clinical experience has shown that in certain diseases a high percentage of cures is obtained by the administration of two or more drugs than is the case when either is used alone even in higher doses. Among these are penicillin and streptomycin in subacute bacterial endocarditis caused by *streptococcus fecalis*, streptomycin and paraminosalicylic acid in tuberculosis, aureomycin or other broad spectrum antibiotics with dihydrostreptomycin in brucellosis and finally penicillin with a sulfonamide in actinomycosis.

The administration of two drugs simultaneously can have any one of a number of possible effects. First they may be indifferent, that is no effect is noted upon the action of either drug. If the total effect of both drugs is equivalent to the sum of their actions, then their effect is additive. If on the other hand the final action is even greater than the expected total of their individual effects, they are synergistic. In general, two or more bactericidal agents will provide more killing power than the same total of any one agent, probably by combining their different pathways of action. Finally, if the observed result is less than when each drug is used independently, one agent is antagonistic to the other. Such interference may be due to the fact that most antibiotics are usually effective against actively dividing bacteria and it is possible for a bacteriostatic drug to prevent the activity of a bactericidal agent by stopping or slowing the metabolic processes involved.

All the above mentioned possibilities do and can occur in practice. Fortunately, the last effect, although clearly demonstrable in the test tube and in experimental infections, is extremely rare and only one such occurrence has so far been reported clinically (8). The tube test readily lends itself to the determination of the sensitivity of any organism to a combination of any number of antibiotics, the proportions of each component of the mixture being altered and tested at will. Thus by means of this technique it can be ascertained whether the effect of two or more drugs in any proportions will prove to be additive, synergistic, antagonistic or indifferent *in vitro*. This of course does not necessarily indicate that the same effects will take place in the body, but the laboratory findings may support or negate this possibility and provide the clinician with suggestive data for his consideration.

A drawback to the tube test method is that it requires material and skills only available in large laboratories. It may therefore be necessary to resort to a simpler

technique such as the "disc" method. Hospitals or laboratories with facilities and personnel to perform even a modest amount of bacteriology can effectively employ the disc method. It is simple, involves comparatively little effort or expense and can be easily learned. Petri culture dishes are evenly inoculated with the organism or mixture of organisms under study and discs saturated with different antibiotics of varied concentrations are then applied to the surface of the seeded plates. After appropriate incubation the dishes are examined for the presence or absence of a clear zone, devoid of bacterial growth, around each individual disc. When the bacteria under investigation are sensitive to a particular concentration of a specific antibiotic contained on the disc, a clear zone around it will be present. This represents absence of growth around the disc as a consequence of diffusion of the antibacterial agent into the surrounding medium which then exerts its inhibitory effect. On the other hand, if the organisms are resistant to the action of the drug, no clear zone will be present and the inoculated organisms grow right up to the disc margin.

Discs are available commercially in a variety of sizes, shapes and concentrations covering a broad range. However, some of these concentrations are considerably higher than those ordinarily found in the body. To provide information of the greatest value to the physician only those concentrations that actually correspond to the level usually found in the concerned body fluid, such as blood, urine or spinal fluid after appropriate doses of antibiotics should be selected. No attempt should be made to compare the efficacy of different antibiotics by assessing the sizes of their zones of inhibition. Too many extraneous factors exert an influence, among which are the inherent diffusibility of each antibiotic that may or may not be related to its activity, the type of medium employed and the size of the bacterial inoculum surrounding each disc. All in all, this method can be of considerable value provided the concentrations tested correspond to the levels actually found in the body and if the results are merely reported qualitatively as Sensitive or Resistant. When compared to the tube test the disc method has many obvious shortcomings. It does not provide the precise quantitative information of the former, the effect of combinations cannot be measured with it and it is unsuitable for the determination of bactericidal endpoints. In spite of these limitations adequate information can be obtained with it for the successful treatment of a good number of infections. Where one is faced with more difficult treatment problems and when additional information provided by the more complex test is essential resort to a laboratory equipped and capable of performing the latter procedure may be obligatory.

GUIDE TO CLINICAL PROGRESS

Progress after treatment or the lack thereof can best be measured with the assistance of the laboratory. The disappearance of microorganisms originally present on smear and culture together with the subsidence of clinical signs and symptoms offers the most reliable index of cure. On the contrary, persistence of the infecting organisms even though the infection has apparently subsided clinically denotes a lack of a completely satisfactory response and usually calls for

a change or modification of therapeutic tactics. This may take the form of a change of drug or type of preparation, an increase in dosage or frequency of administration or perhaps a change in the route of administration. These changes, based upon data supplied by the laboratory, may very well then produce the desired effect.

Where no organisms have been isolated and where the diagnosis has been based upon deviations of the serological pattern, reversal towards normal may represent a favorable trend. This applies especially to syphilis where the patient usually presents himself at a time when clinical signs are minimal or absent. Without the laboratory, the physician is unable to properly judge the effects of therapy. In this as in many other infectious diseases, periodic follow-up laboratory examinations are obligatory before the final results of treatment can be correctly assessed and the patient pronounced as cured. Otherwise the patient may be apparently cured and therapy discontinued only to have him suffer a recurrence at a later date. Laboratory investigation offers the best criterion regarding complete eradication of the infection so that therapy can then be safely discontinued.

DETERMINATION OF ANTIBIOTIC LEVELS OF BLOOD AND OTHER BODY FLUIDS

Although these assays are ordinarily not indicated or performed in routine cases, information regarding the local concentration may sometimes prove of considerable value in resolving some difficult therapeutic problems. Administration of identical doses of an antibiotic preparation by the same route and at the same time intervals does not necessarily produce identical blood levels in the same or a number of different patients. The degree of absorption, the fate of the drug in the body and the rate of excretion all exert an influence. Published figures merely represent a statistical mean of the levels produced in a group of subjects but actually there may be considerable variation in a single individual and between individuals. Nausea, vomiting and diarrhea are not infrequent side effects following the administration of aureomycin, terramycin or chloramphenicol and at times it is difficult to ascertain with certainty how much of the prescribed medication has actually been absorbed. The existence of renal disease or malfunction may alter normal excretion and the exact concentration available in the body to exert its effect may be hard to tell. As a matter of fact penicillin clearance is a good index of kidney function and has been so employed as a test. Thus these assays may furnish a clue regarding abnormal absorption or excretion thereby explaining some therapeutic failures and lead to corrective measures.

It is not always possible to measure the concentration of antibiotic at the site of infection, but estimation of blood levels may prove of importance. Diffusion into the tissues is in part a function of blood concentration (9) and where penetration is a problem, for example in fibrotic or necrotic lesions, it may be necessary to produce high blood levels to enhance penetration into the focus. Laboratory tests can determine whether or not the desired high blood levels are or are not actually being reached. At other times it may be advisable to discover whether or not the antibacterial agent has penetrated into or is being excreted by

a particular system or organ. Testing the appropriate body fluid or tissue may then provide the desired information.

The antibiotic level assays are set up within certain ranges in the laboratory. Selection of these ranges depends upon the antibiotic, preparation, dose, frequency and route of administration, and is based upon the usual experience of the laboratory in similar situations. When the laboratory is provided with this pertinent information, the tests can be set up within the expected range of concentration. Without this it is obliged to explore a wide area which leads to the unnecessary expenditure of time and materials and of much greater importance, the loss of very valuable time. When there is a demand for these tests time is usually an important factor. Such cooperation can enable the laboratory to expedite its reports thereby proving of even greater service to the clinician.

REFERENCES

1. BARBER, M., AND ROZWADOWSKA-DOWZENKO, M.: Infection by Penicillin-Resistant Staphylococci, *Lancet*, 2: 641, 1948.
2. FORBES, G. B.: Infection with Penicillin-Resistant Staphylococci in Hospital and General Practice, *Brit. Med. Journ.*, 2: 569, 1949.
3. SPINK, W. W.: Clinical and Biological Significance of Penicillin-Resistant Staphylococci Including Observations with Streptomycin, Aureomycin, Chloromycetin and Terramycin, *J. Lab. & Clin. Med.*, 37: 278, 1951.
4. SCHNEIERSON, S. S.: Changes in Bacterial Sensitivity to Aureomycin and Chloramphenicol in the Course of the Past Three Years, *J. Lab. & Clin. Med.*, 40: 48, 1952.
5. GINSBERG, I. A., AND HYMAN, G. A.: Combined Aureomycin and Streptomycin Therapy of *Pseudomonas Aeruginosa* (*Bacillus Pyocyaneus*) Meningitis; With a Case Report, *Ann. Int. Med.*, 37: 194, 1952.
6. TROEN, P., AND DI CAPRIO, J. M.: *Pseudomonas Aeruginosa* Meningitis: Report of a Case Treated with Terramycin, *U. S. Armed Forces Journ.*, 3: 1629, 1952.
7. WAISBREN, B. A., CARR, C., AND DUNNETTE, J.: The Tube Dilution Method of Determining Bacterial Sensitivity to Antibiotics, *Am. J. Clin. Path.*, 21: 884, 1951.
8. LEPPER, M. H., AND DOWLING, F. H.: Treatment of Pneumococcal Meningitis with Penicillin Compared with Penicillin plus Aureomycin: Studies Including Observations on an Apparent Antagonism Between Penicillin and Aureomycin, *A.M.A. Arch. Int. Med.*, 88: 489, 1951.
9. GERBER, I., SCHWARTZMAN, G., AND BAEHR, G.: Penetration of Penicillin into Foci of Infection, *J.A.M.A.*, 130: 761, 1946.

STUDIES IN MYASTHENIA GRAVIS: EDROPHONIUM CHLORIDE (TENSILON) TEST AS A NEW APPROACH TO MANAGEMENT

KERMIT E. OSSERMAN, M.D., LAWRENCE I. KAPLAN, M.D. AND GERALD BESSON, M.D.

From the Myasthenia Gravis Clinic and the Departments of Medicine and Neurology, The Mount Sinai Hospital, New York, New York

A new approach to the management of myasthenia gravis has been evolved through the use of edrophonium chloride (Tensilon) as a testing agent to permit the clinician to judge the effectiveness of therapy.

Historically, Tensilon was introduced as a drug for the treatment of myasthenia gravis (1). However, it was found to be unsatisfactory for this purpose because of the short duration of its beneficial effects. Tensilon, because of its speed of action, became an excellent rapid diagnostic test for the diagnosis of myasthenia gravis (2). In these studies the difference in responses to the Tensilon test in the myasthenic treated with either Prostigmin or octomethylpyrophosphoramide (OMPA) led to the clarification of the symptom of weakness, one type being myasthenic in origin, the other being cholinergic due to overtreatment with anticholinesterase (antiChE) therapy (3).

A Tensilon test is performed by injecting 1 cc. (10 mg.) of the drug intravenously. Within 30 to 60 seconds several effects are observed. These consist of: 1) changes in the muscle strength; 2) the presence or absence of fasciculations*; 3) the presence or absence of side reactions. In performing this procedure on myasthenic patients under treatment, three types of responses are noted: 1) *Myasthenic* (in the inadequately treated patient); 2) *Adequate* (ideal state); 3) *Cholinergic* (in the overtreated patient) (Table I).

The *myasthenic* reaction is one in which there are subjective and objective findings of increased strength without fasciculations or side reactions (2), (3). In order for a response to be called *cholinergic*, there are the following minimal requirements: 1) the patient complains of feeling worse; 2) increased weakness is noted by the examiner; 3) side reactions may vary from very mild to very severe and may become the dominant feature. Fasciculations may be seen, but their absence does not preclude a *cholinergic* response if the other factors are present.

An *adequate* response is the ideal in the treatment of a myasthenic patient. When Tensilon is given to a normal patient, he will show fasciculations and mild side reactions, but no change in strength. The perfectly controlled myasthenic should respond in this same manner. There is a wide range of *adequate* responses which may vary from the *cholinergic* side of adequate to the *myasthenic* side of *adequate*. The response may show some features of both extremes. Muscarinic effects may predominate on the *cholinergic* side and be evidenced by lacri-

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* Fasciculation: visible, involuntary contraction or twitching involving a group, bundle, cluster, or fasciculus of muscle fibers.

mation or salivation, while the nicotinic effects may be on the *myasthenic* side as evidenced, for example, by an equivocal increase in ability to swallow or an equivocal decrease in ptosis. The important single feature of the *adequate* response, however, is that any change noted, be it in strength, side reactions, or fasciculations, is a very mild one.

It soon became evident that there was a relation between the time of the last dose of antiChE medication and the responses to the Tensilon test. The interpretations would depend upon this time lapse. To determine this factor, myasthenic patients were first tested with Tensilon in a basal state. In the basal state the patient clinically exhibits the severest form of the disease because no effective

TABLE I
Responses to Tensilon test

	MYASTHENIC	ADEQUATE	CHOLINERGIC
<i>Muscle strength</i>	Increased	No change	Decreased
Ptosis			
Diplopia			
Dysphonia			
Dysphagia			
Dysarthria			
Respiration			
Limb strength			
<i>Fasciculations</i>	Absent	Present or absent	Present or absent
Orbicularis oculi			
Facial muscles			
Limb muscles			
<i>Side reactions</i>	Absent	Minimal	Severe
Lacrimation			
Diaphoresis			
Salivation			
Abdominal cramps			
Nausea			
Vomiting			
Diarrhea			

antiChE medication has been given for a variable period. The patient was then given a dose of his antiChE medication, either Prostigmin (bromide or methylsulfate) or OMPA, and Tensilon tests were repeated at regular time intervals.

Before serial testing could be evaluated, it was necessary to exclude accumulated antiChE effect of Tensilon itself when frequently administered. Tensilon has only 1/100 of the antiChE effect of Prostigmin on the eel esterase (4). Ten milligrams of Tensilon is injected into patients, which is 10 to 20 times the amount of Prostigmin used; therefore, Tensilon exhibits 1/10 to 1/5 of the antiChE effect of Prostigmin. When the antiChE effect of Tensilon was tested in our patients, we found that there was a measurable depression, although inconstant. After an injection of Tensilon, we did serial tests at 5 to 10 minute intervals on

the red cell esterase (5). The effect apparently was dissipated in 30 minutes. Therefore, when we first attempted to find a time relationship between the Tensilon test and the trial dose of antiChE medication, the test was performed at 30 minute intervals. It was found clinically that with this interval there was an additive effect from the Tensilon. Therefore, the procedure was done on an hourly basis and did not show this effect.

Patients attending the Myasthenia Gravis Clinic and the wards of the Mount Sinai Hospital who were being treated with Prostigmin and/or OMPA were tested with Tensilon. A single or a serial test at one hour intervals for a period of three hours was done in order to determine the proper dosage and the frequency of administration necessary for the management of each patient.

This series of patients includes myasthenics who were difficult to control. We have termed them "brittle," borrowing the use of the term from a comparable group of "brittle" diabetics. A "brittle" myasthenic is one whose requirements and time of dosage varies abruptly and erratically demanding frequent changes. Particular attention was paid to those cases in which respiratory weakness was a feature.

In the use of the longer-acting antiChE drug, OMPA, it is best to perform the test once daily just before the next dose is due. The drug is slowly absorbed and excreted and all the information needed for transferring and maintaining the patient may be obtained by this method. When OMPA and Prostigmin are used in combination, the last dose of Prostigmin should be given at least three hours before the Tensilon test is performed. The effects of the OMPA medication can then be elicited by the test. After the patient has been transferred to OMPA, the Tensilon test can be performed at the regular clinic or office visits to evaluate his status.

With the shorter-acting Prostigmin (bromide or methylsulfate) serial testing is of particular value. It helps to determine the duration of activity of medication and can be used to determine fairly accurately the amounts of the drug to be prescribed (Table II). Medication can be stopped as in Case 2 when the patient was seen to be in a remission, or the dosage and frequency can be increased as in Case 3. This latter patient was taking large amounts of Prostigmin and became so weak that she could not raise her hands to feed herself. Clinically it seemed that cholinergic weakness had developed. Serial Tensilon testing proved the patient required even larger doses of Prostigmin and improvement followed this change in dosage. Case 7 was a "brittle" myasthenic. The titration type of testing was used on this patient to obtain the upper and lower limits of dosage.

In most instances it was found that patients returned to their basal tests at the end of three hours, showing that effects of the dose of Prostigmin had been dissipated. When the response is *adequate* for the first and second hours and becomes *myasthenic* at the end of the third hour, the dose is correct and the timing is probably correct, but the patient may be better managed if the interval is shortened by perhaps a half hour. If the response is *myasthenic* throughout, the dose should be increased. If the response is *cholinergic* throughout, the dose should be decreased. If the response is *cholinergic* at the end of the first hour,

TABLE II

CASE #	SEX	AGE	DEGREE OF MYASTHENIA	DAILY PROSTIGMIN SCHEDULE*	TIME SINCE LAST DOSE	CLINICAL STATUS OF PATIENT BEFORE TESTING	RESPONSE TO BASAL TENSILON TEST	AMOUNT OF PROSTIGMIN DOSE TESTED
1	F	61	Mild	Syrup 2 cc. q 4h (p.o.)	6 hr.	Very weak	Myasthenic	Syrup 4 cc. (p.o.)
2	F	21	Very mild	1½ tab. t.i.d.	3	Good	Adequate	½ tab.
3	F	38	Severe	Methylsulfate 1½ cc. (s.c.) q 3h	3	Very weak (probably overtreatment)	Myasthenic	Methylsulfate 2 cc. (s.c.)
4	M	54	Moderate	1 tab. q 3h	5	Fair	Adequate	Methylsulfate 1 cc. (s.c.)
5	F	46	Severe	2½ tab. q 3h	5	Very weak	Myasthenic	Methylsulfate 1¼ cc. (s.c.)
6	M	46	Severe	3 tab. q 3½h	4	Poor	Myasthenic	3 tab.
7a	M	48	Severe	2 tab. q 2h	2	Poor	Myasthenic	Methylsulfate ¼ cc. (s.c.)
b	M	48	Severe	2 tab. q 2h	2	Poor	Myasthenic	Methylsulfate 1½ cc. (s.c.)

RESPONSE TO TENSILON TEST			REMARKS	CHANGES IN MANAGEMENT
1 Hour	2 Hours	3 Hours		
Adequate	Adequate	Myasthenic	Test dose adequate	Dose increased to 4 cc. q 3h p.o.
Cholinergic	Cholinergic	Cholinergic	Became weaker during testing	Patient in remission. Medication discontinued
Adequate	Adequate	Myasthenic	Markedly improved during testing	Parental dose increased to 2 cc. q 2½ hrs.
Cholinergic side of adequate	Myasthenic side of adequate	Myasthenic	Was cholinergic ½ hour after dose of medication	Change indicated to 1 tab. q 2½h as test dose twice usual dose
Adequate	Adequate	Myasthenic	Improved during first 2½ hours of testing	Dose increased in frequency to every 2½ hours
Adequate to cholinergic	Myasthenic	Myasthenic	Patient first felt better about 1½ hrs. after test started	Dose changed to 2½ tab. every 2 hrs.
Myasthenic	Myasthenic	Myasthenic		At ¼ cc. patient was very myasthenic
Cholinergic	Cholinergic	Cholinergic	Test used to determine extremes of dosage	At 1½ cc., cholinergic response was elicited, therefore, patient was treated with ¾ cc. q 2 to 3 hrs.

The usual antiChl² dosage for the purposes of this titration were ignored. On the basis of prolonged observation of the patient, a test dose estimated to be adequate was given. It must be emphasized that the serial tests were an indication of the patient's response to the test dose, and not to the prior medication.

* 4 cc. syrup = 1 tablet (15 mg. bromide) approximately equivalent to ½ mg. methylsulfate (½ cc.)

becoming *adequate* to *myasthenic* in the second or third hour, then the dose should be decreased and the timing changed.

It is necessary to distinguish between the results of serial testing in the usual *myasthenic* from the results in the "brittle" *myasthenic*. It is in the management of the "brittle" *myasthenic* that serial testing is not only helpful, but indispensable. While it is often possible to predict the sequence of events in the average *myasthenic* by a single Tensilon test done at any time, in the "brittle" type of patient a single test cannot tell what he may have been doing one hour before or will do one hour hence.

The majority of *myasthenics*, however, as shown in table II will have a limited number of possible responses over a three-hour period. A single test will often indicate which set of serial responses is present without the complete titration being necessary. Serial testing is the ideal method to be used to establish optimal time and dosage of medication in the management of the *myasthenic* patient. However, the practical value of a single test may be noted:

1. Much time can be saved by avoiding repeated serial testing.
2. In the treatment of the patient with OMPA, serial testing is of no value.
3. At times of crisis an immediate appraisal of the nature of the weakness, *myasthenic* or *cholinergic*, is urgent.

The best time to perform the single test in the average *myasthenic* is at the end of the second hour after Prostigmin has been administered. At this time, if the patient's response is *myasthenic*, he will not improve. If his response is *adequate*, it is safe to assume that his response was not *myasthenic* at one hour and that the dosage schedule need not be altered, although it may be either *myasthenic* or *adequate* at three hours. If the response is *cholinergic*, there is no question that the dosage must be reduced and this would be true even though he were to become *adequate* at three hours.

In fact, the single Tensilon test performed at one hour after Prostigmin dose is almost as valuable as that performed at the second hour. However, in the serial test in which the response is *adequate* at one hour, but *myasthenic* at the second and third hours, the need for increased dosage of medication or decreased time interval would not be revealed by a test at the one-hour level. The advantage of the two-hour over the three-hour test is that in most patients the effects of Prostigmin have been dissipated by the third hour. The nature of the responses cannot be inferred in the first and second hour by a single test. Whenever possible the serial test should be done since it provides more complete information about the status of the patient and since there may be other variations in the responses of the patient which have not yet been determined by the limited number of titrations performed in this study.

Perhaps the most valuable use of the single Tensilon test in the management of *myasthenia gravis* is for the simple, accurate and rapid clarification of the cause of respiratory crisis. There were five cases of respiratory difficulty in this group of *myasthenic* patients. The management of these cases demonstrated the development of our understanding of the Tensilon test from the first case where the test was not available to the fifth case where it was invaluable in the proper handling of a severe "brittle" *myasthenic*.

CASE REPORTS

Case 1 was treated before the development of the Tensilon method for management. This patient was a 49 year old male with "brittle" myasthenia gravis for five years, regulated with both OMPA and Prostigmin. One evening he aspirated his dinner and developed respiratory distress. He was seen by his local physician who administered an injection of Prostigmin. The patient became cyanotic and unconscious. Artificial respiration was given and he was rushed to a local hospital where suction through bronchoscopy was employed and artificial respiration continued. We were consulted at this time and immediately ordered a respirator. There was a three-hour delay in the delivery of the respirator. During this delay, we ordered that a continuous i.v. containing 3 mgs. of Prostigmin be started. Tremendous amounts of bronchial secretion were formed. Frequent use of suction through a bronchoscope and atropine sulfate was employed. While the patient was being transferred to the respirator, he died. In retrospect, the conclusion that the patient was in a myasthenic state, needing further Prostigmin may have been erroneous. However, a clinical appraisal was all that was available at that time.

In the other four cases we used the Tensilon test to determine whether cholinergic or myasthenic causes were the basis for the respiratory weakness.

Case 2 was a white male, aged 44, known myasthenic of two months' duration with a bulbar onset. He was admitted for transfer to OMPA and in the course of his therapy he suddenly became weaker. This was very early in our experience with the Tensilon test. A misinterpretation of the test as a *myasthenic* response was occasioned by the lack of fasciculations and Prostigmin was administered in addition to OMPA. We now know that lack of fasciculations may exist in all three responses in the myasthenic patient. Following the injection of Prostigmin, the patient developed a clinically evident cholinergic crisis with respiratory arrest and, in spite of all efforts to reverse his cholinergic state, the patient died within three hours.

Case 3 was a white female, aged 43, and a known myasthenic of 14 years' duration requiring 300 mgs. Prostigmin daily. She was admitted to the hospital for transfer to OMPA. The day before she was due to be discharged from the hospital, an intercurrent viral pneumonia developed and she developed marked respiratory weakness. A Tensilon test was performed and showed typical *myasthenic* weakness, with improvement of her respirations. One mg. of Prostigmin was injected subcutaneously and the patient improved. However, 1½ hours later, she was again in marked respiratory distress. Since she had respiratory embarrassment on the basis of her pneumonia in addition to her severe myasthenia, it was felt that the temporary use of the respirator was justified. Twelve hours later she was withdrawn from the respirator and replaced on Prostigmin. Virus pneumonia cleared and the patient was restandardized on Prostigmin bromide. This is the same patient as case 5 in Table II.

Case 4, a white female aged 43, had a malignant thymoma and myasthenia gravis. Despite increasing amounts of OMPA and Prostigmin, the Tensilon tests showed continued *myasthenic* responses. The patient was deteriorating rapidly from her malignancy: respirations became shallow, and she was placed in a respirator, dying the next day. Her course was fulminating, death ensuing three months after the onset of her first symptoms. At no time did she display any *cholinergic* reactions. This patient died of her malignancy complicated by uncontrollable myasthenia gravis confirmed by the consistently *myasthenic* responses to the Tensilon test.

Case 5 was a "brittle" type of bulbar myasthenia gravis. This patient had been treated with OMPA at another hospital and had been in a respirator on four previous occasions. He had a functioning tracheotomy and an indwelling Levine tube when admitted to our hospital. Before we had an opportunity to establish optimal dosage and timing, he developed respiratory weakness after aspirating his dinner. This patient was a physician who had been in many crises, became alarmed with his respiratory weakness, and demanded an injection of Prostigmin. From our previous experience we had learned that the clinical ap-

praisal of weakness was undependable. A Tensilon test was performed and unequivocally indicated that the weakness was not the result of myasthenic crisis. The response was on the *cholinergic* side of *adequate*. On the basis of this test alone, despite the pressure from the patient for Prostigmin, it was withheld. He was treated for his cholinergic state with grains $\frac{1}{50}$ of atropine sulfate injected intravenously to decrease the salivation and bronchial secretion. Aspirated material was suctioned. Both of these procedures eased his respiratory distress within ten minutes. Although a respirator was immediately available throughout this course of events, the patient went through the night without needing it. No Prostigmin was given during this period on the basis of the Tensilon response. The patient was permitted to return to a controllable myasthenic state. By the next morning, the Tensilon test revealed a typical *myasthenic* response. Now the problem revolved about the establishment of an optimal dose and schedule. The clarification of the amount of Prostigmin necessary to induce a cholinergic state became important and since he was "brittle" in his previous responses to medication, it was decided to place him in a respirator as a precautionary measure. Serial Tensilon testing with varying doses of Prostigmin was then performed without danger to the patient when cholinergic respiratory distress developed. This is patient 7 from Table II. By means of this titration we were able to treat this patient by using $\frac{3}{4}$ mg. of Prostigmin on a two to three hour basis.

The frequent use of the single and serial Tensilon tests enabled us to manipulate his dosage so that he was kept in a state of relatively adequate control. It enabled us further to discharge him from the hospital and to make adjustments of his dosage on an outpatient basis. He had lost forty pounds in body weight prior to the admission to our hospital. Within seven weeks from admission he regained twenty-five pounds. As his activity increased, and as the effects of the previously administered OMPA wore off, his needs for Prostigmin increased. Despite the fact that his needs increased from $\frac{3}{4}$ mg. q 3h to 2 mgs. q 2h, a 400% increase, there was never any serious difficulty encountered in this relatively rapid change of dosage because we used the Tensilon test as a guide.

DISCUSSION

As our experience with the use of edrophonium chloride (Tensilon) as a testing agent broadens, we have discovered that the management of myasthenia gravis no longer depends upon the trial and error technique of varying the interval and dosage of medication solely with a clinical appraisal of the patient. The Tensilon test has proven to be an invaluable adjunct in the evaluation of the treatment requirements of a myasthenic. As a result of our increasing familiarity with its values, we can no longer conceive of the proper management of a myasthenic, especially the "brittle" type, without Tensilon, no more than we would attempt to manage a diabetic without access to urinary sugar determinations. In a previous paper we have described the *myasthenic*, *adequate*, and *cholinergic* responses to Tensilon (3). These reactions, indicating respectively, undertreatment, adequate treatment, and overtreatment with antiChE drugs, form the basis for the plan of management in myasthenia gravis. In early trials with the use of the Tensilon test in the treated myasthenic, it was found (quite logically in retrospect) that different types of responses in the same individual depended on the variation of the interval between a given dose of Prostigmin and the performance of the test. These observations led us to believe that there was available a method for the predictable and almost quantitative management of myasthenia gravis. Therefore, a series of clinical titrations was begun in a group of myasthenics under varied therapeutic regimens. Serial Tensilon tests, performed at hourly intervals for three hours after a single test dose of Prostigmin, were completed.

The results of these tests, outlined in Table II, indicated the changes necessary in timing and dosage of Prostigmin to correct the management of the patient.

Furthermore, an analysis of the results of serial testing showed very clearly that if it were necessary to choose an optimal time for the performance of a single Tensilon test as a means of evaluating contemplated changes in medication, this time would be two hours after a given dose of Prostigmin. With a test performed at this interval, adequate therapeutic insight is possible without the complete serial test. This does not apply to the "brittle" myasthenic whose requirements vary so erratically that unpredictable fluctuations will be demonstrated only by a serial test. The single test is also valuable in the management of the patient under OMPA therapy (performed optimally twelve hours after medication) and indispensable in the emergency appraisal of the nature of weakness in a respiratory crisis. The use of the Tensilon test in the management of a respiratory case is shown in the five cases presented.

These cases clearly demonstrate the value of the use of Tensilon in the management of myasthenia gravis. In the first case when the Tensilon test was not available, management depended upon the uncertain clinical evaluation of the patient. In the second case, the value of the Tensilon test in a crisis became evident to us, although our understanding of the *cholinergic* response was not yet clear. In the last three cases, the Tensilon test was a dependable guide in the appraisal of the nature of a crisis, provided a rapid estimate of the situation, and predictably governed subsequent management of the patient.

BIBLIOGRAPHY

1. a) WESTERBERG, M. R., MAGEE, K. R., AND SHIDEMAN, F. E.: Effect of 3-Hydroxy Phenyl dimethylethylammonium Chloride (Tensilon) in Myasthenia Gravis, Univ. Hosp. Bull., Ann Arbor 17: 311 (Sept.) 1951. b) WESTERBERG, M. R., MAGEE, K. R., AND SHIDEMAN, F. E.: Effect of 3-Hydroxyphenyl Dimethylethylammonium Chloride (Tensilon) in Myasthenia Gravis, Neurology, 3: 4, pp. 302-305 (April) 1953.
2. OSSERMAN, K. E., AND KAPLAN, L. I.: Rapid Diagnostic Test for Myasthenia Gravis, J.A.M.A., 150: 265 (Sept. 27) 1952.
3. OSSERMAN, K. E., AND KAPLAN, L. I.: Studies in Myasthenia Gravis: The Use of Edrophonium Chloride (Tensilon) to Differentiate Myasthenic from Cholinergic Weakness. To be published A.M.A. ARCH. of neur.
4. RANDALL, L. O.: Anticurare Action of Phenolic Quaternary Ammonium Salts, J. Pharmacol. & Exper. Therap., 100: 83, 1950.
5. OSSERMAN, K. E.: Unpublished data.

THE SIGNIFICANCE OF BILATERAL ABNORMALITY IN THE ELECTROENCEPHALOGRAM*

MORTIMER OSTOW, M.D., MED. SC.D., AND HANS STRAUSS, M.D.

The neurosurgeon, faced with the responsibility for the treatment of a patient with a brain tumor, is grateful for whatever information his colleagues can provide to establish the presence and location of such a tumor. When the electroencephalographer is able to report the presence of a clearly demarcated region of slow abnormality and indicate its location on a diagram, he is usually offering information which is useful in establishing or confirming a diagnosis. When, however, the electroencephalogram shows a bilateral abnormality it is generally considered to be much less useful. Nevertheless, even the bilaterally abnormal electroencephalogram may prove to be of value.

The translation of data from the linear oscillations of the electroencephalographic record into diagnostically significant data is ordinarily performed in two steps. The first consists of a translation of the record into a statement about the presence and nature of any physiologic disturbance. This task is the responsibility of the electroencephalographer. The second step consists of the translation of the physiologic statement into one concerning the diagnostic probabilities, both etiologic and structural. Although it is the task of the electroencephalographer and the neurophysiologist to work out the technique of this transformation, in any individual case this task is best performed by the clinician who can fit these data into the whole collection of information derived from the history, examination, and other laboratory procedures. The proper evaluation of electroencephalographic data requires a knowledge of the correlations between the electroencephalogram on the one hand and clinical data on the other, together with a knowledge of the physiologic principles which constitute the basis of electroencephalography. It is the purpose of this paper to present some tabulated data from which an attempt will be made to derive some useful generalizations.

In the recent British symposium on electroencephalography edited by Hill and Parr (1), W. A. Cobb suggests that bilaterally synchronous delta activity (1-4 per second) indicates the presence of a tumor in the region of the epithalamus, upper mid-brain, or posterior fossa. He also suggests that posterior fossa lesions produce bilateral delta activity only by virtue of mechanical distortion of the mid-brain; "all the bilateral rhythms, therefore, form one group." Cobb attributes bilateral theta (4-7 per second) activity to lesions "in or near the thalamus, or more broadly adjacent to the third ventricle; it is seen with suprasellar tumors, basal tumors encroaching on the mid-line, dilatation of the third ventricle, and so on." He acknowledges that lesions of this latter group may also be associated with the slower delta waves. One of the earliest studies of the electroencephalographic changes in patients with neoplasms of the posterior fossa was that of Smith, Walter, and Laidlaw (2). These authors describe posterior

* From the Departments of Neurology and Neurosurgery, The Mount Sinai Hospital and Beth Israel Hospital, New York, N. Y.

slowing in patients with cerebellar tumors and in one patient a tumor of the third ventricle. One of the most carefully documented studies of posterior fossa tumors is that of Rheinberger and Davidoff (3). These authors found posterior slowing bilaterally in all of five cases of eighth nerve tumor and in one patient with a cerebellar abscess. Other space occupying lesions of the posterior fossa give rise to bilateral abnormality either anteriorly or at the mastoid electrodes. Although the records are not entirely symmetrical, at the points of maximum abnormality, they are usually symmetrical. In a recent presentation before the American Electroencephalographic Society, Bagchi, Lam, and Kooi (4) indicated that they have found bilateral synchrony and motor or frontal localization or occasionally occipital localization. In contradistinction to Rheinberger and Davidoff (3), Bagchi and his coworkers (4) believe that in those posterior fossa lesions which are unilateral, the electroencephalogram is contralaterally more abnormal. However, it is mentioned that these findings may be encountered also in patients with tumors in the third ventricle and in some acute cerebral vascular conditions; nor could they distinguish between extra-axial and intra-axial lesions.

In 1946 (Margaret) Lennox and Brody (5) observed paroxysms of slow waves in 17 proven and 14 probable cases of subcortical diseases, including lesions of the basal ganglia, thalamus, cerebellum, hypothalamus, and pons. They inferred that the bouts of slow waves in epileptics probably arise in deep structures.

In brief, most authors find in cases of posterior fossa space-occupying lesions, bilaterally synchronous slowing either anterior, temporal or posterior in location with occasional accentuation of the abnormality on one side or the other. All observers acknowledge that differentiation between posterior fossa lesions and other midline lesions, especially tumors of the third ventricle, cannot be made by use of the electroencephalogram.

OBSERVATIONS

A. Series from Mount Sinai Hospital. 1. Symmetrical vs. asymmetrical slowing. The following material is based upon the tabulation of 2500 electroencephalograms in patients with definitely established diagnoses at the Mount Sinai Hospital. In Table I is listed the incidence of slow abnormalities among 203 patients with hemisphere tumors and 93 patients with either posterior fossa or midline tumors. It will be noted that the incidence of normal records is considerably lower among patients with hemisphere tumors than among those with posterior fossa, pituitary or suprasellar tumors. Among the posterior fossa tumors, angle tumors are associated with abnormal electroencephalograms much less frequently than are cerebellar tumors. In fact, an electroencephalographic abnormality was encountered in only 20 per cent of patients with angle tumor. Table I also shows that among patients with supratentorial tumors, only 5% showed symmetrical abnormalities in the electroencephalogram while 68% showed asymmetric slowing. In sharp contrast, patients with posterior fossa, pituitary, suprasellar or other midline tumors showed symmetrical abnormalities much more frequently than asymmetric slowing. Of all patients having either a tumor of the posterior fossa or midline, 31% showed symmetrical slow activity and only 3% presented asymmetric slowing. Moreover, this preponderance of symmetric over asymmetric slowing is similar in the posterior fossa, pituitary, suprasellar and the midline groups. In short, given a patient with an intracranial tumor, if there is a bilaterally symmetrical electroencephalographic abnormality, the chance that the tumor is located in one of the cerebral hemispheres is very small. On the other hand, the probability that the tumor is

either in the midline supratentorially or in the posterior fossa is strong. However, the presence of a symmetric abnormality does not permit differentiation between the members of the latter group.

In Table II the electroencephalographic patterns of patients with tumors are compared with the records of patients falling into several other diagnostic categories. It can be seen that among patients with hemisphere tumors there is a clear cut preponderance of slow asymmetric over slow symmetric abnormalities and that among patients with posterior fossa or midline tumors there is clear-cut preponderance of symmetric over asymmetric abnormalities. Symmetric abnormalities are also clearly the most common finding among

TABLE I

The relation between the location of tumors and the distribution of slow activity in the electroencephalogram

	NUMBER OF PATIENTS	SYMMETRICAL SLOWING AND/OR BURSTS	PARASYMMETRICAL SLOWING	ASYMMETRICAL SLOWING	NORMAL RECORDS
		%	%	%	%
Supratentorial hemisphere tumors.	203	5	11	68	15
Posterior fossa tumors.....	55	24	18	2	56
Cerebellar tumors.....	25	36	36	0	28
Angle tumors.....	27	15	4	4	78
Pituitary and suprasellar tumors...	31	38	3	3	55
Other midline tumors.....	7	57	14	14	14

TABLE II

The relation between the nature of the brain disease and the distribution of slow abnormality in the electroencephalogram

	NUMBER OF PATIENTS	SYMMETRICAL SLOWING AND/OR BURSTS	PARASYMMETRICAL SLOWING	ASYMMETRICAL SLOWING	NORMAL RECORDS
		%	%	%	%
Supratentorial hemisphere tumors.	203	5	11	68	15
Midline and posterior fossa tumors	93	31	13	3	52
Degenerative disease.....	43	44	0	2	56
Vascular disease.....	198	17	6	6	56
Meningitis.....	26	20	27	19	35
Subarachnoid hemorrhage.....	48	27	27	17	29

patients with degenerative disease of the brain. However, among patients with cerebral vascular disease although symmetric abnormalities are more common than asymmetric ones, there is no striking preponderance as there is in the diagnostic categories listed above; that is, neither a symmetric nor asymmetric abnormality can be considered "characteristic" of vascular disease. In cases grouped under the next two diagnostic categories, subarachnoid hemorrhage and meningitis, it is known that large areas of the surface of the brain are affected. In these two categories it is evident that parasymmetric slowing is as common as, or more common than either symmetric or asymmetric slowing. Moreover, the incidence of records with symmetric, parasymmetric or asymmetric slowing is not very different so that it is not possible to consider any of these three types of records as characteristic of subarachnoid hemorrhage or meningitis. (In those tabulations, a record with asymmetric

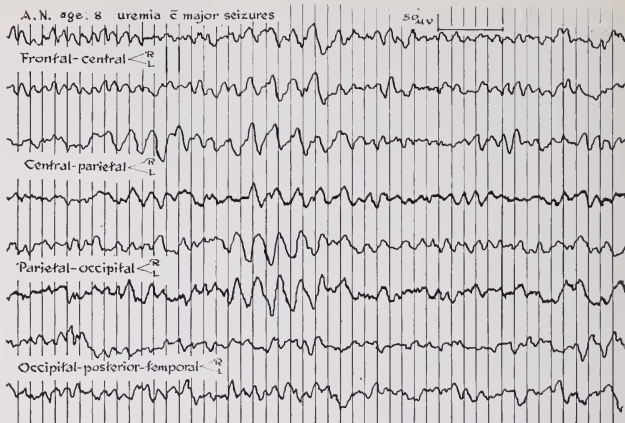


FIG. 1. Bilaterally synchronous bursts of 3 per second activity in the record of an 8 year old boy with major seizures probably due to uremia.

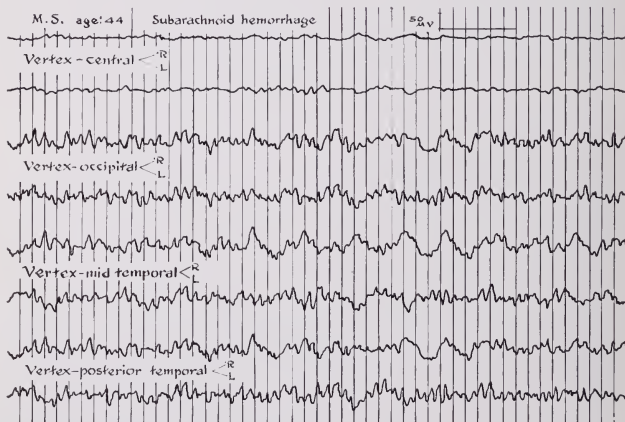


FIG. 2. One to two per second activity appearing diffusely in the record of a 44 year old patient with subarachnoid hemorrhage. There is an equal amount of slow activity on the two sides but the slow waves are not bilaterally synchronous.

slowing is defined as one in which the ratio of amount of slow abnormality of the side with the major abnormality as compared with the side with the minor abnormality is at least 1.5. When asymmetry is less pronounced or when there is an equal amount of slow activity on each side but the activity is not bilaterally synchronous, the record is called parasymmetrical (figs. 1 and 2.) In summary, although a symmetrically slow record is characteristic of patients with midline or posterior fossa tumors and also of patients with degenerative disease of the brain, there is no type of record which is characteristic of patients with vascular disease of the brain or with widespread disturbance of the surfaces of the brain as in meningitis or subarachnoid hemorrhage.

2. *Paroxysmal vs. non-paroxysmal slowing.* In Table III are listed those conditions in which bursts or paroxysmal activity appear with conspicuous frequency. Only symmetrical bursts of slow activity are considered in this tabulation. These are seen, for example, in patients with posterior fossa or midline tumors and rarely in patients with tumors of one of the cerebral hemispheres. They are seen in patients with degenerative or congenital disease of the brain. By contrast they are not seen in patients with chronic subdural hematoma or with brain abscess. It is interesting to observe that among patients studied within three months after a head injury, non-paroxysmal slowing is much more frequent than

TABLE III

The relation between the nature of the brain disease and the presence of symmetrical bursts of slow activity in the electroencephalogram

	NUMBER OF PATIENTS	SYMMETRICAL SLOWING WITHOUT BURSTS	SYMMETRICAL SLOWING WITH BURSTS	BURST ALONE	BURSTS ON HV ALONE
		%	%	%	%
Midline and posterior fossa tumors	93	23	2	6	0
Degenerative disease	43	23	9	12	0
Early trauma	96	21	3	3	0
Late trauma	41	7	0	17	5
Idiopathic epilepsy	309	2	0	81	11
Congenital disease	51	25	0	14	0

bursts, while among patients examined later than three months after a head injury, bursts are encountered much more frequently than non-paroxysmal slowing. Bursts are the characteristic finding in patients with idiopathic epilepsy; in this series they are encountered in 81% of the 309 patients with that diagnosis. In sharp contrast, non-paroxysmal slowing is seen in only 2% of those cases. Therefore, although most of the patients who get to an electroencephalographic laboratory and have bilaterally synchronous bursts in their records are patients with idiopathic epilepsy, this type of record is also encountered in patients with posterior fossa or midline tumors, congenital or degenerative, or even vascular disease of the brain, or post-traumatic encephalopathy (figs. 3, 4, 5, and 6). Hence, although the appearance of bilaterally synchronous bursts of slow activity in the electroencephalogram is always an abnormal sign, this finding alone does not permit an etiologic diagnosis. No tabulation has been made of those patients showing an increase in bilaterally synchronous paroxysmal slowing on hyperventilation, when the resting record is abnormal, but Table III does reveal that 5% of patients with late post-traumatic encephalopathy and 11% of patients with idiopathic epilepsy show bilaterally synchronous bursts during hyperventilation although the resting record is entirely normal. Although it is likely that the mechanism for the production of bursts on hyperventilation is not very different from the mechanism for the production of bursts in the spontaneous record, in this series no patient with a brain tumor showed bursts during hyperventilation and a normal spontaneous record.

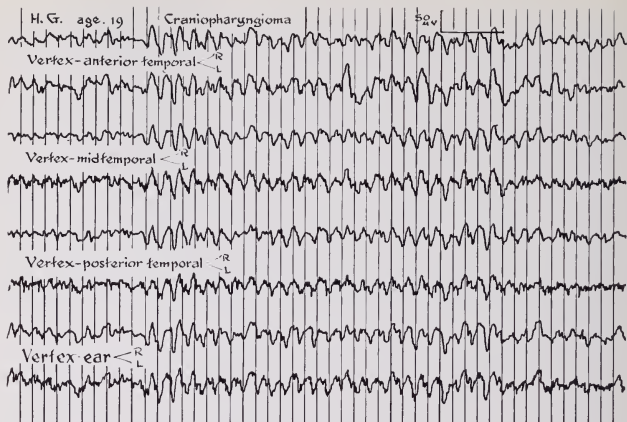


FIG. 3. A 6 second burst of regular high voltage bilaterally synchronous 4 per second activity in the record of a 19 year old patient with a craniopharyngioma.

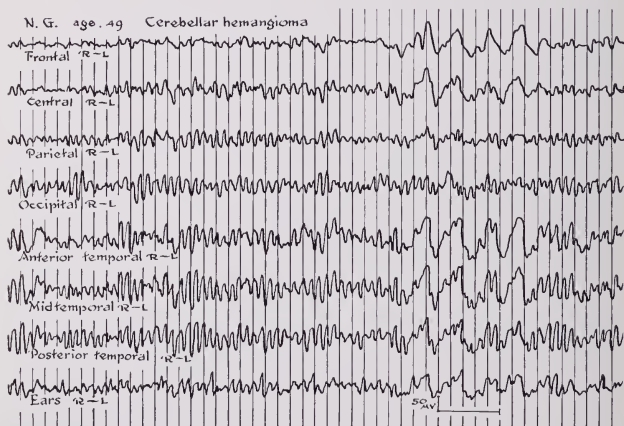


FIG. 4. A 2 second burst of high voltage 2 per second activity in a 49 year old patient with a cerebellar hemangioma with internal hydrocephalus. Note the anterior and temporal distribution. In other portions of the record it was seen that these bursts were bilaterally synchronous.

In Table IV the same data presented in Table III are rearranged so that those diagnostic categories with the lowest number of normal records are listed first and those diagnostic categories with the highest number of normal records are listed last. Only those diseases

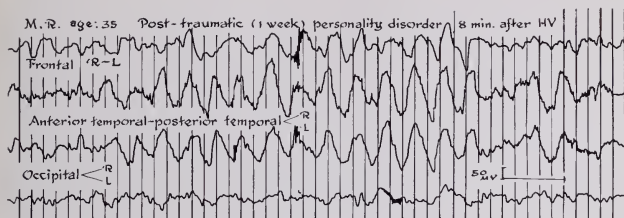


FIG. 5. A second burst of high voltage bilaterally synchronous 2 per second activity appearing during the eighth minute after cessation of a two minute period of hyperventilation in a 35 year old patient with severe personality disturbance following severe head injury with concussion.

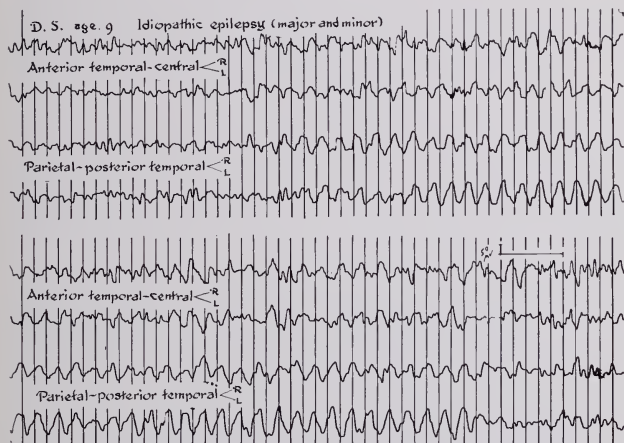


FIG. 6. A 14 second burst of high voltage bilaterally synchronous 4 per second activity in a 9 year old patient with major and minor seizures of unknown origin (idiopathic epilepsy). In other portions of this record there were clear cut bursts of 3 per second spike and wave activity. Note that the bursts are more prominent posteriorly than anteriorly.

which have a progressive course are listed. On reading down the column headed "Bursts Alone", one will observe that although the total amount of abnormality decreases, the incidence of symmetrical bursts increases. If one may assume that a low incidence of normal records implies considerable physiologic disturbance, and conversely that a high incidence of normal records implies minimal physiologic disturbance, then one may infer that the smaller the degree of physiological disturbance, in patients with some progressive

diseases of the brain, the more frequently one encounters bursts in the electroencephalogram, and the greater the degree of physiologic disturbance, the less frequently one encounters bursts in the record. One might assume, therefore, that symmetrical bursts are an early sign and symmetrical non-paroxysmal slow activity a later sign of the same or of related basic physiologic disturbances.

B. Series from Beth Israel Hospital. Among a smaller group of patients from Dr. Leo M. Davidoff's service at the Beth Israel Hospital, essentially similar data were obtained although the records were read quite independently. Thus, of 43 patients with hemisphere tumors, 6 or 14% have normal records. Of 14 patients with sellar, suprasellar or third ventricle tumors, 5 or 36% have normal records. Of 15 patients with cerebellar tumors or posterior fossa obstruction of other cause, 4 or 27% have normal records. Again, as in the Mount Sinai series, patients with hemisphere tumors show for the most part an asymmetrical slow abnormality, very few showing symmetrical abnormality. On the other hand, the patients with midline or posterior fossa tumors characteristically show symmetrical slowing; only 3 of 34 showing an asymmetric abnormality. Bilateral bursts are encountered more often

TABLE IV

The relation between the incidence of bursts in the electroencephalogram and the incidence of normal records among patients with various diseases of the brain

	NUMBER OF PATIENTS	SYMMETRICAL SLOWING WITHOUT BURSTS	SYMMETRICAL SLOWING WITH BURSTS	BURSTS ALONE	NORMAL RECORDS
		%	%	%	%
Other midline tumors	7	57	0	0	14
Cerebellar tumors	25	28	8	0	28
Subarachnoid hemorrhage.....	48	23	2	2	29
Meningitis.....	26	12	4	4	35
Pituitary and suprasellar tumors..	31	32	0	6	55
Vascular disease.....	198	10	4	3	56
Degenerative disease	43	23	9	12	56
Meningovascular syphilis.....	23	13	0	9	78
Angle tumors.....	27	0	0	15	78

among patients with midline or posterior fossa tumors than among patients with hemisphere tumors. As in the Mount Sinai series, no patients with a normal resting record but with bursts on hyperventilation were found to have a brain tumor in the Beth Israel series, with two exceptions. The first was an adult patient with clearly demonstrable internal hydrocephalus by ventriculography but with no abnormality evident at the time of operative exploration of the posterior fossa. The second was a 39 year old man who in June, 1951 complained of increasingly frequent dizzy spells and occasional nausea of six months duration. The electroencephalogram, when the patient was resting, was normal. On hyperventilation there were clear cut high voltage bisynchronous bursts of 3 per second activity, but only when the patient was fasting. His symptoms became progressively more prominent during the summer. On 11 October 1951 the electroencephalogram showed slight but definite 1-2 per second activity posteriorly. The only response to hyperventilation was a slight increase of the posterior slowing, but a fasting record was not obtained. A ventriculogram performed on 12 October 1951 showed slight symmetrical dilation of the ventricular system and at operation, Dr. E. Feiring found a papilloma of the choroid plexus of the fourth ventricle. Another interesting fact which appears in the Beth Israel data is that, even among those records which are abnormal in the resting state, bursts appear on hyperventilation only in the group of patients with midline and posterior fossa tumors but not among pa-

tients with hemisphere tumors. This is all the more striking since patients with hemisphere tumors may show a diffuse but non-paroxysmal slow response to hyperventilation or accentuation of focal slowing on hyperventilation.

Although patients with hemisphere tumors, for the most part, show an electroencephalographic abnormality over those regions of the brain affected by the lesion, it is interesting to note that the bilaterally slow abnormality appearing in those with midline or posterior fossa tumors, may be diffusely distributed, or most prominent anteriorly, or most prominent posteriorly. There is a tendency for the bursts to be localized anteriorly and non-paroxysmal slowing to be greater posteriorly, but there are several exceptions. As primarily occipital tumors are relatively uncommon, it appears that posteriorly located foci of slow abnormality are much more often indicative of midline or posterior fossa tumors than of occipital lobe tumors. Of 43 patients with hemisphere tumors, only 2 show posterior foci, one of which is asymmetrical; of 14 patients with midline tumors, 4 show posterior foci of which none is asymmetrical; of 20 patients with posterior fossa tumors, 3 show posterior foci; none is asymmetrical. Thus in the presence of a symmetrical or parasymmetrical, paroxysmal or non-paroxysmal focus of slow abnormality located posteriorly, one is much more likely dealing with a midline or posterior fossa tumor than with an occipital lobe tumor. A similar statement cannot be made about more anteriorly located foci since parasymmetrical foci located anteriorly are much more often a sign of hemisphere rather than of midline or posterior fossa tumors.

Slowing of alpha activity was also examined in this series. Of 43 patients with hemisphere tumors, 5 show alpha frequency of less than 8 per second. In contrast, of 28 patients with midline or posterior fossa tumors, 11 show an alpha frequency of less than 8 per second. Slowing of the alpha frequency occurs about four times as often among patients with midline or posterior fossa tumors than among patients with hemisphere tumors.

CASE REPORTS

It was inferred from Table IV above, that the type of physiologic disturbance encountered in patients with midline or posterior fossa tumors was more apt to induce symmetrical bursts of slow activity when the disturbance was mild or early, and more likely to produce non-paroxysmal bilateral slow activity as the disturbance became more pronounced. It will be interesting to see whether this inference can be confirmed in serial studies of individual cases.

Figure 7 includes samples of two electroencephalographic recordings in the same case. This patient is a 44 year old woman who was admitted to Dr. Leo M. Davidoff's service at the Beth Israel Hospital 20 October, 1950. She complained of headache, stumbling and vomiting. Neurologic examination showed some cerebellar signs but there was no papilledema. Ventriculography revealed symmetrical dilatation of the entire ventricular system as far back as the middle portion of the aqueduct. At this time the electroencephalogram showed bilaterally synchronous bursts and non-paroxysmal slow activity varying in frequency from 2-6 per second. There was some tendency for the bursts to be more prominent anteriorly and somewhat faster in frequency than the non-paroxysmal slow activity which was more prominent posteriorly. Sub-occipital craniectomy was performed on 25 October. A cyst and mural nodule were encountered in the right half of the cerebellum and on pathological examination the diagnosis of hemangioblastoma was made. The patient recovered and on the 9th of November, about two weeks following operation, the second electroencephalogram was recorded; the same type of slow abnormality was present but it was considerably less prominent. In summary, early electroencephalographic changes are demonstrated in a patient with internal hydrocephalus due to a cerebellar hemangioblastoma. These changes consisted of bilaterally synchronous bursts anteriorly and slow activity posteriorly. Post-operatively there was a decrease in the amount of slow activity without much change in its nature.

Figure 8 shows samples of serial electroencephalograms in the case of an 8 year old boy who had had a tremor of the right hand for three years. On examination there was a posi-

tive MacEwen sign and low grade papilledema. Ventriculography disclosed considerable symmetric dilatation of the entire ventricular system up to the aqueduct and some visualization of anterior portion of the aqueduct. The electroencephalogram on 24 November showed a large amount of non-paroxysmal 1.5-3.0 per second activity at both occipital regions; it was not always symmetrical and perhaps more marked on the left. Following hyperventilation there were several high voltage bursts of 3 per second activity as well as

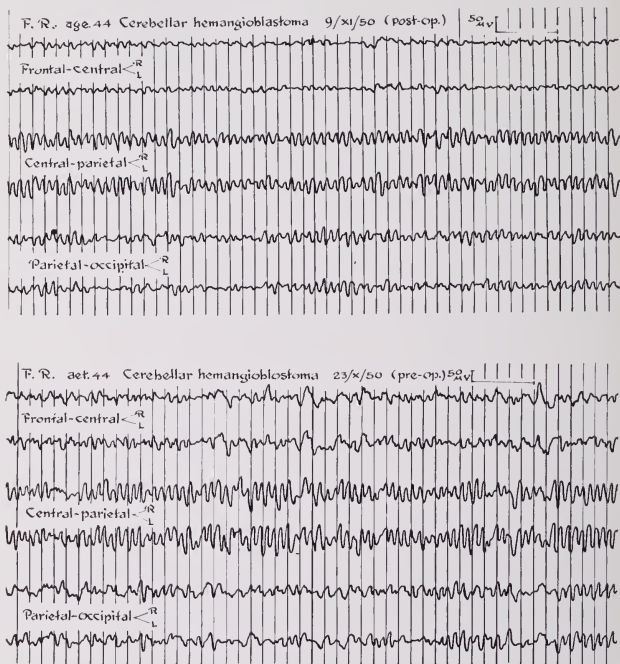


FIG. 7. Pre-operative and post-operative records of a 44 year old patient with cerebellar hemangioblastoma and internal hydrocephalus. In the pre-operative record there is sporadic, serial and paroxysmal slow activity most of which is absent from the post-operative record.

exaggeration of the posterior slowing. A sub-occipital craniectomy was performed on 5 December 1950; no tumor was encountered but the rate of escape of fluid into the cisterna magna after the injection of saline into the left lateral ventricle indicated at least partial obstruction of the aqueduct. A Torkildsen procedure was performed, and the patient recovered. On discharge there was some improvement in the tremor. An electroencephalogram performed on 18 December, two weeks after operation, showed a diminution of alpha frequency to 6-7 per second. However, the most striking change was a substitution of clearly

demarcated high voltage bursts posteriorly for the non-paroxysmal slowing present pre-operatively. A month later the alpha frequency had returned to its preoperative level and the posterior slowing was still paroxysmal in character. At this time the patient was much more sensitive to hyperventilation and could not continue beyond one minute whereas previously he had been able to hyperventilate for two minutes. Moreover, the response to

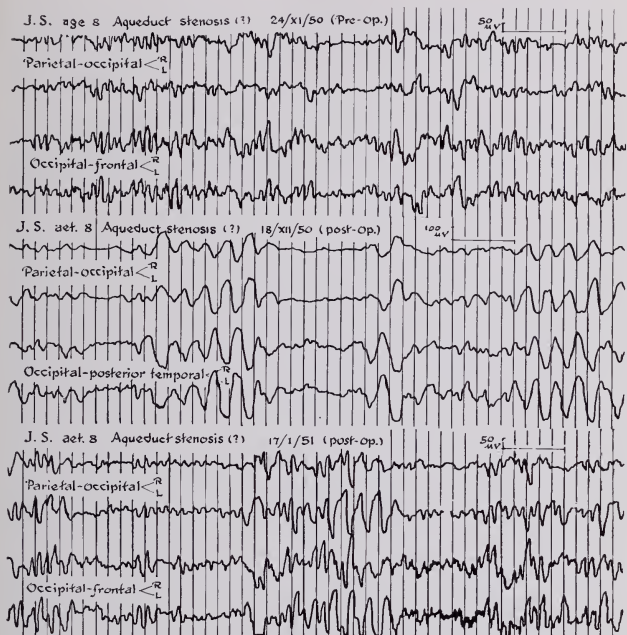


FIG. 8. A pre-operative and two post-operative records in the case of an 8 year old boy with internal hydrocephalus but without tumor of the posterior fossa. The operation consisted of exploration and of relief of the internal hydrocephalus by the Torkildsen procedure. Pre-operatively there is almost continuous 1-2 per second activity posteriorly not bilaterally symmetrical. Post-operatively in the same distribution there are clear cut bursts of high voltage 3 per second activity.

hyperventilation after one minute was much more pronounced than it had been preoperatively. In summary, a patient is described with non-paroxysmal posterior slowing before relief of internal hydrocephalus and clear cut bursts of slow activity posteriorly after operative relief of the hydrocephalus. Moreover, after operation the patient was much more sensitive to hyperventilation.

The final patient in this series (fig. 9) is a 55 year old man who was admitted to the hospital in February, 1951 with a history of mental confusion of about one week's duration.

He was apathetic and sleepy and early papilledema was present; there were some reflex changes and a stiff neck. On 27 February an electroencephalogram showed almost no activity within the alpha range; there was a continuous background of fairly regular 4-5 per second activity, diffuse and symmetrical. The most striking change was a series of high voltage bilaterally synchronous bursts of 2-3 per second activity most prominent anteriorly and

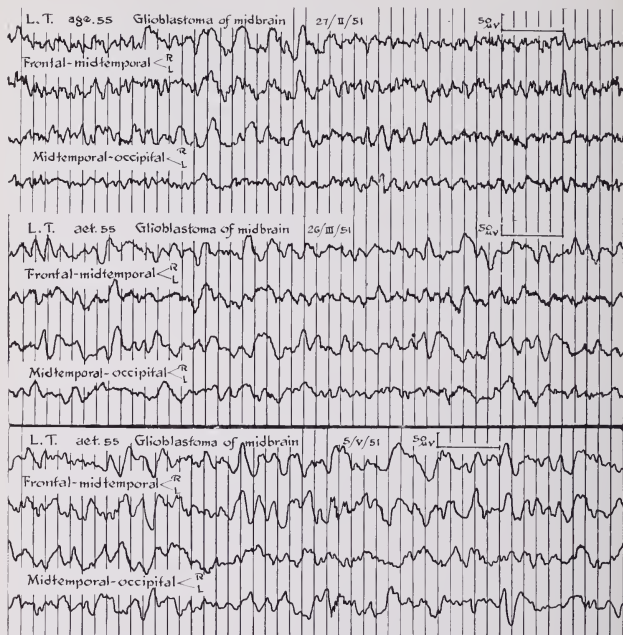


FIG. 9. Serial records in the case of a 55 year old man with a glioblastoma of the midbrain causing progressively increasing internal hydrocephalus. The initial strip shows a bilaterally synchronous burst of 2 per second activity and a background of 5-6 per second activity. In the subsequent strips there are no bursts, the slow activity becomes slower and less symmetrical.

temporally. A ventriculogram performed a few days later showed dilatation of the entire ventricular system up to the midportion of the aqueduct. No mass was encountered on exploration. The patient's condition did not vary significantly in the ensuing weeks. An electroencephalogram on 26 March, one month after the initial tracing, showed no bursts but a large amount of non-paroxysmal 1-3 per second activity diffuse sometimes, but not always bilaterally synchronous. Lamina terminalis puncture was performed after a second ventriculography on 13 April and showed possibly some slight increase in the internal hydrocephalus. The patient improved somewhat after this procedure but about two weeks

after operation he had a severe generalized convulsive seizure. The clinical condition continued to deteriorate and an electroencephalogram one week after the seizure showed continuous irregular $\frac{1}{2}$ to 5 per second activity, diffuse and often asymmetrical. The patient died one week later and post mortem examination revealed the presence of a glioblastoma in the region of the aqueduct. In summary, a patient with internal hydrocephalus due to obstruction of the aqueduct was observed over a period of 11 weeks during which time his course deteriorated. The initial electroencephalogram showed bilaterally synchronous bursts anteriorly and temporally; later tracings showed no bursts but diffuse slow abnormality, not always symmetrical.

SERIAL CHANGES WITH DEVELOPING AND RECEDING INTERNAL HYDROCEPHALUS

From these three examples one may attempt a reconstruction of the sequence of electrophysiological disturbances following obstruction of the outflow of fluid from the ventricular system beyond the third ventricle. The first change is the appearance of bilaterally synchronous bursts of slow activity which may be as slow as 2 per second or as fast as 6 per second. These bursts may appear either anteriorly, temporally, or posteriorly. The bursts are increased in prominence and prevalence during hyperventilation but as the internal hydrocephalus increases, the response to hyperventilation is obliterated. Occasionally bursts will not appear at all but non-paroxysmal slow activity will appear posteriorly bilaterally, often more pronounced on one side. In some cases both bursts and posterior slowing may develop simultaneously. As the hydrocephalus increases, the bursts disappear and are followed by bilateral slowing, diffuse in distribution and showing progressively less synchrony. When the initial disturbance consists only of posterior slowing, with further progress the posterior slowing becomes generalized and the frequency further diminishes. If internal hydrocephalus recedes, either spontaneously or as a result of surgical intervention, the sequence of electroencephalographic changes is reversed.

DISCUSSION

Diffuse vs. bilaterally synchronous slowing. It may be concluded that in dealing with an electroencephalogram which shows bilateral abnormality, it is important to know whether or not the abnormality is bilaterally synchronous. Only when the abnormality is not synchronous on the two sides is one justified in inferring the presence of a diffuse cerebral disturbance. Records with nonsynchronous bilateral abnormality are termed parasymmetrical and have been found especially in patients with meningitis, subarachnoid hemorrhage, or vascular disease.

In 1944 and again in 1948, Pacella, Kopeloff, Barrera and Kopeloff (6, 7), in their observations upon the effects of chronic focal irritation of the cerebral cortex, reported that in a few cases an electroencephalographic abnormality appeared on the side contralateral to the side of irritation some time after the ipsilateral focus developed. Such contralateral foci are referred to as "mirror foci". Examination of their records discloses that the abnormalities on the two sides were not synchronous (except after the intravenous injection of metrazol). Although we have been aware of these observations we have never been convinced that contralateral electroencephalographic slowing was not the result of actual contralateral physiologic disturbance as for example might be caused by mechanical pressure effects, edema, vascular disturbance or involvement of midline structures. To our knowledge, the problem of mirror foci has never been properly evaluated in clinical electroencephalography.

History of concept of diencephalic abnormality. No matter how diffusely distributed or how persistent the slow abnormality may be, so long as it is bilaterally synchronous, it is evident that it is arising not from the cortex underlying the recording electrodes but rather from some structure within the central nervous system which has access simultaneously to both cerebral hemispheres. During the past decade, and especially during its latter half, a great deal has been learned about the location of such structures. The problem of the source of bilaterally synchronous abnormality was encountered early in the electroencephalographic studies of epilepsy. In 1941, Jasper and Kershman (8) and Jasper (9) working with Penfield suggested that the bilaterally synchronous spike and wave discharge of classical petit mal as well as some other bilaterally synchronous rhythms seen in the epilepsies, had their origin in a pacemaker in the diencephalon. Meanwhile in 1944 Walter and Dovey (10), in 1945 Cobb (11) and in 1946 Lennox and Brody (5) pointed out that bilaterally synchronous slow abnormalities could be seen not only in the electroencephalograms of epileptics but also in the records of patients with deep subcortical tumors usually in the neighborhood of the third ventricle. In 1947 Jasper and Droogleever-Fortuyn (12), by stimulating the region of the intralaminar nuclei of the thalamus in the cat at 3 per second, were able to produce bilaterally synchronous waves often with spikes, resembling the clinical petit mal electroencephalographic seizure. They inferred that the intralaminar region of the thalamus on either side, especially near the mid-line, had access to and could synchronize the activity of the two cerebral hemispheres. Jasper (13) focused attention in 1949 on what he called "the thalamic reticular system" which had the power to synchronize or block electrical activity of the entire cortex on both sides. In the same year Lindsley, Bowden and Magoun (14) demonstrated in the isolated cat brain that bursts of high voltage slow waves occurred synchronously on the two sides after injury to the mid-brain or basal diencephalon. In 1950 Gastaut and Hunter (15) observed that following the intravenous injection of metrazol in the cat, rhythmic response to intermittent photic stimulation suddenly appeared over the entire cortex and many regions of the thalamus whereas before the injection of metrazol the response had of course been limited to the visual cortices. The latency of the diffuse response was 25 milliseconds in the thalamus and 30 milliseconds in the cortex. They concluded that under certain circumstances it was possible for visual stimuli to escape from the visual pathways in the thalamus into thalamic circuits that had access to the entire cortex of both sides. Lindsley, Schreiner, Knowles and Magoun (16) in 1950 again observed that bilaterally synchronous slow activity appeared in cats with chronic lesions of the diencephalon. In 1951 McLardy (17) took tissue with those proposing the existence of a diffuse projection system in the thalamus and suggested that the structure responsible for diffusing slow activity over the entire cortex was a complex of intralaminar nuclei which served only to diffuse activity within the thalamus so that all specific projection nuclei were simultaneously activated. Although much remains to be learned about specific structures and mechanisms, it seems to have been fairly well established that there are structures in the diencephalon that have access simultaneously to both sides of the cerebral cortex.

Following the lead of these experimental observations, it has become the practice in many electroencephalographic laboratories to interpret bilaterally synchronous slow activity as an indication of disturbance in function of the diencephalon. Among the nonsurgical conditions giving rise to this type of disturbance, idiopathic epilepsy is of course the most frequent. This abnormality is seen in metabolic disturbances and occasionally as a result of drug action. It may appear in patients without organic disease but with certain severe psychic disturbances e.g., patients with psychopathic personality (18). It is well known by this time as a result of the work of Lennox, that individuals with no clinical disease but with a family history of epilepsy, may show bilaterally synchronous bursts of slow abnormality in their electroencephalograms. Such individuals may or may not at some time in their lives have one or more seizures.

Diencephalic abnormality after electric shock treatment and after head injury. A condition in which bilaterally synchronous bursts of slow activity are an almost constant finding is the physiologic disturbance following the application of electro-convulsive treatments. Here the development of bilaterally synchronous frontal followed by temporal and then diffuse bursts of 3-6 per second activity is a fairly commonplace observation. Even before the abnormality appears in the resting record, bursts appear on hyperventilation. As more treatments are given, sensitivity to hyperventilation increases markedly and the individual episodes of slow activity in the resting record last longer and longer so that ultimately the record becomes continually and diffusely but always bilaterally synchronously slow. Roth (19) recently pointed out that intravenous pentothal injection would often elicit bilaterally synchronous bursts in patients who had received too few electric shocks to show this change in the spontaneous record. However, as more drug was injected or as the number of electric shock treatments increased, the voltage of the slow activity diminished and its regularity decreased, so that it began to lose its paroxysmal nature. Callaway (20) observed that further electric shock treatment after high voltage bisynchronous 2-3 per second activity had appeared, resulted in obliteration of this slow activity, and upon cessation of treatment, several days were required before slow activity recurred only to disappear again later. These facts are reminiscent of the sequence of changes which we reconstructed from our clinical observations of patients with internal hydrocephalus; namely, initially increased sensitivity to hyperventilation, bilaterally synchronous bursts, usually anteriorly, substituted later by irregular not always symmetrical slower activity, fairly diffusely. We also are reminded at this point of the difference noted in the tabulation of the Mount Sinai series between patients seen soon after head injury and patients seen later after head injury. In the early group the abnormality, though largely symmetrical or parasymmetrical included few bursts, while in the later group the incidence of bursts was much greater than the incidence of non-paroxysmal slow activity. It is only in the later group that bursts appeared on hyperventilation, even when the spontaneous record was normal. One may infer that in head injury as with electric shock, there is injury to the diencephalon. With head injury it is manifested initially by bilateral but non-paroxysmal slow activity and later, with improvement, by paroxysmal slow activity. During the course of a series of electric shock treat-

ments, the order is reversed. In this discussion those instances of head injury with focal abnormality due to cerebral contusion or laceration are excluded.

Diencephalic abnormality with internal hydrocephalus. It is now possible to understand why tumors in the region of the third ventricle or any disease entities giving rise to physiologic disturbances of the diencephalic structures can produce bilaterally synchronous slow activity. That leaves the problem of the mechanism of electroencephalographic abnormality in patients with posterior fossa lesions. Since the changes are essentially similar whether the lesion is a space occupying one or whether it is merely an obstruction of the outflow of the ventricular system, the most likely explanation is that the resulting internal hydrocephalus is in some way responsible for the abnormalities. It should be mentioned at this point that others who have written on this subject have failed to find a direct correspondence between internal hydrocephalus and electroencephalographic abnormality. Moreover, some patients in this series with clearly established internal hydrocephalus have normal electroencephalograms. Williams in 1940 (21) could find little relationship between the height of increased intra-cranial pressure, the level of consciousness and electroencephalographic changes. He found that reducing intra-cranial pressure by lumbar drainage seldom changed the electroencephalogram. He did discover that the intravenous injection of hypertonic solutions produced prompt improvement in the electroencephalogram no matter what happened to the intra-cranial pressure. He inferred that the abnormality was due to edema of the white matter with physiological interruption of cerebral pathways. Stewart in 1941 (22) performed some experiments on cats in which he was able to distinguish between an increase in intra-cranial pressure produced by ventricular obstruction and that produced by interference with the absorption of cerebro-spinal fluid. In the latter case there was no disturbance of the electroencephalogram but when the pressure was increased because of ventricular obstruction, there was slowing. He suggested that the slow waves might be due to "tension on the white fibres of the brain during hydrocephalus." Scarff and Rahm in 1941 (23) reported that slow waves disappeared immediately on tapping the ventricles. In the case of the 8 year old boy with internal hydrocephalus but no mass in the posterior fossa whose records we demonstrated above, the electroencephalogram changed from the non-paroxysmal to the paroxysmal type after ventricular drainage by the Torkildsen procedure. Therefore, it is probably correct to say that although there are some patients with internal hydrocephalus who show no electroencephalographic change in others, electroencephalographic changes parallel and therefore are probably dependent upon the degree of internal hydrocephalus or possibly its rate of development. We may go one step further and say that since the electroencephalographic changes with hydrocephalus are often exactly the same as those seen with disturbance of diencephalic function whether by third ventricle tumor, head injury, electric shock treatment or other pathogenic agent, one effect of internal hydrocephalus is to produce disturbance of diencephalic function.

Posterior slowing with internal hydrocephalus. We are still left with the problem of the significance of the posterior focal slowing. The early writers suggested that

this might be due to upward pressure of posterior fossa lesions against the occipital lobes. However, this same abnormality is seen even in cases with aqueduct stenosis without a mass in the posterior fossa or with tumors of the third ventricle with internal hydrocephalus. Although posterior slowing is seen in normal young children, or occasionally in children or young adolescents with epilepsy of unknown origin, we have never seen it in any case of brain tumor without internal hydrocephalus. Since the activity in the occipital lobe is usually not paroxysmal and often not even bilaterally synchronous, one possible explanation is that the physical stretching of the ventricular lining accompanying internal hydrocephalus affects the posterior regions first. As illustrated in our third case, ultimately non-synchronous activity becomes widespread over the entire cortex suggesting that ventricular stretching ultimately produces widespread abnormality which is not centrally regulated. This sounds like an attractive theory but of course it fails to account for the situation of our 8 year old boy whose posterior slow activity changed from non-paroxysmal to paroxysmal and bisynchronous and remained posterior. We are forced to infer therefore that at least in some instances the posterior slowing as well as the anterior slowing, is diencephalic in origin. Possibly local abnormality due to ventricular stretching supercedes the diencephalic abnormality first posteriorly and then diffusely. One might imagine, too, that whereas the bursts of mild diencephalic dysfunction are an irritative phenomenon, a greater degree of disturbance permits escape of the cortical tissue from diencephalic control with resulting asynchrony. The observations of both Roth (19) and Callaway (20), cited above, suggesting that increasing amounts of electric shock treatment first increase and then decrease bisynchronous slow activity, would support such a hypothesis.

Slowing of alpha as a sign of diencephalic disturbance. It was demonstrated above that slowing of alpha activity occurs about four times as frequently with lesions of the mid-line or posterior fossa as with tumors of the cerebral hemispheres. Since alpha frequency is normally bilaterally equal, we must infer that that too is regulated in the diencephalon. It follows that disease of the diencephalon can slow the alpha frequency. This is usually the initial change with such metabolic disturbances as hypoglycemia, hypothyroidism or intoxication with sedative drugs. It is occasionally seen also as the initial and sometimes the only sign of a suprasellar mass. Therefore, bilateral slowing of the alpha frequency must be considered not only descriptively but also physiologically an instance of bilaterally synchronous slow activity due to diencephalic disturbance.

In the sequence of electroencephalographic changes described above, alpha slowing does not have a constant place. With suprasellar tumors, hypoglycemia, hypothyroidism and electric shock treatment, alpha slowing occurs early. With head injury, it may never appear. With internal hydrocephalus it occurs early in some cases, late in others.

Diencephalic abnormality and seizures. If it is true that at some point in the course of internal hydrocephalus, due to mid-line or posterior fossa tumor, there is disturbance of diencephalic function physiologically and electroencephalographically indistinguishable from that disturbance seen in patients with con-

vulsive seizures whether attributable to idiopathic epilepsy, to a complication of electroconvulsive treatment or to an aftermath of head injury, why is it that seizures are so infrequent with posterior fossa lesions? At this point we can only guess at the answer. We have had some reason to believe that there is a sensitivity to hyperventilation with mild internal hydrocephalus but not with pronounced internal hydrocephalus. It is possible that the generalized increase in intra-cranial pressure accompanying internal hydrocephalus is responsible both for the suppression of the response to hyperventilation and for the prevention of possible seizures. This may be considered a reasonable guess though we have no evidence to support it.

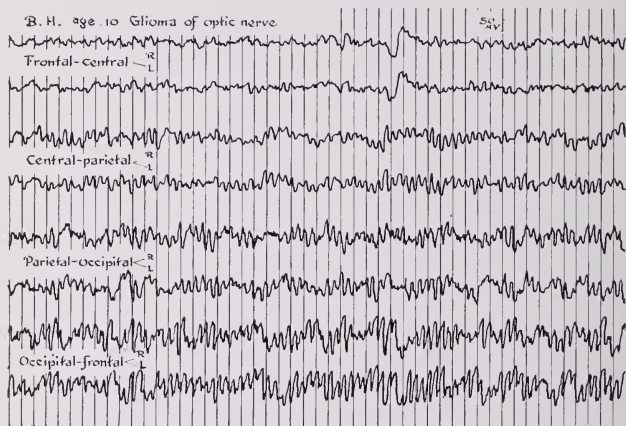


FIG. 10. One to three per second activity appearing posteriorly in the record of a 10 year old boy with a glioma of the optic nerve which extended backwards and upwards into the third ventricle causing internal hydrocephalus.

Illustrative case. The diagnostic significance of bilaterally synchronous slow abnormality in the electroencephalogram may be illustrated by the following case (fig. 10). In December 1950, a 10 year old boy was admitted to Beth Israel Hospital complaining of blindness of the left eye. There was atrophy of the left optic disc, slight proptosis of the left eye and slight left exophoria. The electroencephalogram showed a large amount of moderate voltage non-paroxysmal $1\frac{1}{2}$ to 3 per second activity posteriorly as illustrated in the figure. On clinical grounds it was expected that there was a small tumor of the left optic nerve distal to the chiasm and extending through the foramen into the orbit. At operation it was discovered that the dura was tense and when a needle was inserted through a small stab wound into the anterior horn of the left lateral ventricle a large quantity of clear colorless fluid escaped under increased pressure.

Upon exploration a large tumor was seen in the region of the anterior clinoids, the limits of which could not be defined. Material from the tumor was reported by the pathologist as glioma tissue. In summary, this is the case of a 10 year old boy with the clinical signs and symptoms of a glioma of the optic nerve. The electroencephalogram, however, showed changes similar to those usually seen with internal hydrocephalus. On operation it was seen that the glioma extended backward and upward into the third ventricle causing considerable internal hydrocephalus. For comparison, in the next illustration (fig. 11), a sample of the electroencephalogram of a five year old child with optic nerve glioma extending backwards and upwards into the third ventricle is shown.

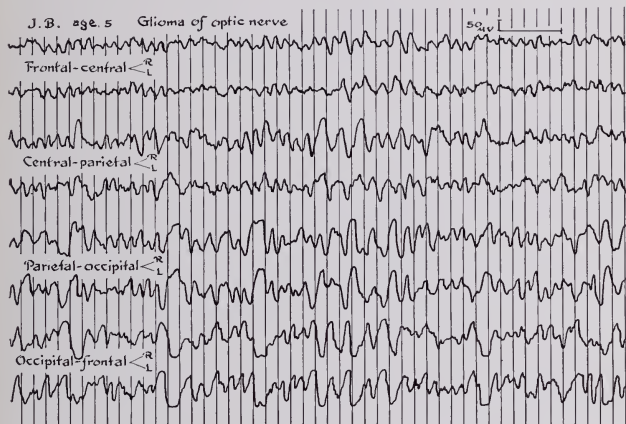


FIG. 11. One to three per second activity appearing posteriorly in the record of a 5 year old girl with a glioma of the optic nerve extending backwards and upwards into the third ventricle causing internal hydrocephalus.

CONCLUSIONS

1. Bilaterally slow abnormality of the electroencephalogram is a sign of diffuse cerebral disease only when the abnormal waves are not bilaterally synchronous.
2. On experimental and clinical ground it may be inferred that bilaterally synchronous slow abnormality (and this includes bilateral slowing of the alpha activity) is a sign of disturbance of diencephalic function.
3. Bilaterally synchronous slow abnormality in the electroencephalogram is seen in patients with convulsive seizures of unknown origin, in patients with toxic or metabolic disturbance of the central nervous system, in patients who have had electro-convulsive treatments or after head injury, and in patients with structural disease of the diencephalic centers of whatever origin including vascular, inflammatory or neoplastic disease.

4. Bilaterally synchronous slow abnormality is also seen in the electroencephalogram with lesions causing internal hydrocephalus due to obstruction of the ventricular outflow.

5. From experimental and clinical observation it can be inferred that, with progressively increasing disease of the diencephalon, the following sequence of changes takes place in the electroencephalogram: a. the appearance of bursts on hyperventilation, b. the appearance of bilaterally synchronous bursts in the resting record, most prominent anteriorly and temporally, c. depression of the hyperventilation response, d. increase in the prevalence of slow activity with a decrease in frequency and regularity. Slowing of alpha activity does not have a constant place in this sequence.

6. This sequence of changes is seen with internal hydrocephalus and therefore that portion of the electroencephalographic response to internal hydrocephalus may probably be ascribed to a disturbing mechanical effect of the hydrocephalus upon the structures neighboring the third ventricle.

7. The posterior non-paroxysmal slowing which is also seen with internal hydrocephalus as well as the irregular asynchronous slow activity which supercedes the bursts as the hydrocephalus progresses, may possibly be ascribed to the mechanical stretching effect of the hydrocephalus upon the ventricular wall, or to release of the cortex from central control or both.

8. When the electroencephalographer reports the presence of diencephalic dysfunction, the distinction between a previously active but now stationary process on the one hand or a currently active process on the other as well as the etiology of the process can be determined only in the light of the full set of data available to the clinician. However, serial electroencephalographic studies can be useful in determining the rate and direction of change in the disease process.

REFERENCES

1. HILL, D., AND PARR, G.: *Electroencephalography*. London, Macdonald, 1950.
2. SMITH, J. R., WALTER, C. W. P., AND LAIDLAW, R. W.: The Electroencephalogram in Cases of Neoplasms of the Posterior Fossa. *Arch. Neurol. and Psychiat.*, 43: 472, 1940.
3. RHEINBERGER, M. B., AND DAVIDOFF, L. M.: Posterior Fossa Tumors and the Electroencephalogram. *J. Mt. Sinai Hosp.*, 9: 734, 1942.
4. BAGCHI, B. K., LAM, R. L., AND KOOL, K. A.: Examination of the Validity of New Empirical Criteria for the Localization of Posterior Fossa Lesions. *EEG Clin. Neurophysiol.*, 3: 383, 1951.
5. LENNOX, M., AND BRODY, B. S.: Paroxysmal Slow Waves in the Electroencephalograms of Patients with Epilepsy and with Subcortical Lesions. *J. Nerv. and Ment. Dis.*, 104: 237, 1946.
6. PACELLA, B. L., KOPELOFF, N., BARRERA, S. E., AND KOPELOFF, L. M.: Experimental Production of Focal Epilepsy. *Arch. Neurol. and Psychiat.*, 52: 189, 1944.
7. KOPELOFF, L. M.: Electroencephalographic Patterns in Experimental Epilepsy. *J. Nerv. and Ment. Dis.*, 107: 99, 1948.
8. KERSHMAN, J.: Electroencephalographic Classification of the Epilepsies. *Arch. Neurol. and Psychiat.*, 45: 903, 1941.
9. PENFIELD, W., AND ERICKSON, T. C.: *Epilepsy and Cerebral Localization*. Springfield, Charles Thomas, 1941.

10. WALTER, W. G., AND DOVEY, V. J.: Electroencephalography in Cases of Subcortical Tumor. *J. Neurol., Neurosurg. and Psychiat.*, 8: 57, 1945.
11. COBB, W. A.: Rhythmic Slow Discharges in the Electroencephalogram. *J. Neurol., Neurophysiol. and Psychiat.*, 8: 65, 1945.
12. DROOGLEEVER-FORTUYN, J.: Experimental Studies on the Functional Anatomy of Petit Mal Epilepsy. Research Publications of the Assoc. Nerv. and Ment. Dis., 26: 272, 1947.
13. JASPER, H. H.: Projection Systems: The Integrative Action of the Thalamic Reticular System. *EEG Clin. Neurophysiol.*, 1: 405, 1949.
14. LINDSLEY, D. B., BOWDEN, J. W., AND MAGOUN, H. W.: Effect Upon the Electroencephalogram of Acute Injury to the Brain Stem Activating System. *EEG Clin. Neurophysiol.* 2: 483, 1950.
15. GASTAUT, H., AND HUNTER, J.: An Experimental Study of the Mechanism of Photic Activation in Idiopathic Epilepsy. *EEG Clin. Neurophysiol.*, 2: 263, 1950.
16. SCHREINER, L. H., KNOWLES, W. B., AND MAGOUN, H. W.: Behavioral and Electroencephalogram Changes Following Chronic Brain Stem Lesions in the Cat. *EEG Clin. Neurophysiol.*, 2: 483, 1950.
17. McLARDY, T.: Diffuse Thalamic Projection to Cortex: An Anatomic Critique. *EEG Clin. Neurophysiol.*, 3: 183, 1951.
18. OSTOW, M., AND OSTOW, M.: Bilaterally Synchronous Paroxysmal Slow Activity in the Electroencephalograms of Non-Epileptics. *J. Nerv. and Ment. Dis.*, 103: 346, 1946.
19. ROTH, N.: Changes in the Electroencephalogram Under Barbiturate Anaesthesia Produced by Electro-convulsive Treatment and Their Significance for the Theory of Ect Action. *EEG Clin. Neurophysiol.*, 3: 261, 1951.
20. CALLAWAY, C.: Slow Wave Phenomena in Intensive Electroshock. *EEG Clin. Neurophysiol.*, 2: 157, 1950.
21. WILLIAMS, D.: The Abnormal Cortical Potentials Associated with High Intracranial Pressure. *Brain*, 62: 321, 1940.
22. STEWART, W. A.: Electroencephalographic Changes Associated with Different Forms of Experimentally Produced Increased Intra-cranial Pressure. *Bull. Johns Hopkins Hosp.*, 69: 240, 1941.
23. SCARFF, J. E., AND RAHM, W. E., JR.: The Human Electroecorticogram. *J. Neurophysiol.*, 4: 418, 1941.

PSYCHOPHYSIOLOGICAL STUDIES OF FISTULOUS OPENINGS INTO THE GASTROINTESTINAL TRACT¹

SYDNEY G. MARGOLIN, M.D.^{2, 3}

When Dr. Moschcowitz honored me by inviting my participation in a series of lectures on Recent Advances in Psychosomatic Medicine, I gladly accepted. I was not only gratified that he thought I had something to say, but I also wished to close a correspondence we had some 12 years ago. At that time, Dr. Moschcowitz sent me a draft of his paper which contained his well-known thesis that the hyperfunctioning of organs and tissues were equivalents of certain mental states, notably the mood disorders (1). I must confess that I dealt destructively with this basically inspired point of view. I was fumbling hopefully with the futile concept of etiological specificity, as though psychosomatic medicine were a collection of clear cut clinical entities. I had not as yet acquired the experiences which later led me to see my conceptual errors. You will realize how great a change has taken place in my views, when I tell you that at the present time I am collaborating in a project in which we are studying the interactions and interdependence of mood states and bodily functions (2, 3). In a sense, therefore, my paper tonight can be regarded as an open letter to Dr. Moschcowitz in which I make my belated acknowledgement of his valuable operational concept. It is my sincere hope that he will recognize what I should have written twelve years ago had I been wiser.

The subject that I shall discuss tonight has been covered in various ways during the past 100 years in books and monographs by many investigators (4, 5, 6, 7). Originally, a fistulous opening into a viscus was regarded opportunely as the simplest and most direct way of examining an organ and its functions. Subsequently, as the role of psychic factors became appreciated, many of the older observations were repeated with this consideration in mind. This form of investigation, namely the so-called psychosomatic approach, is as old as the use of magic in the practice of medicine. It now reappears with the complexities of modern technological devices, and an enormous accumulation of dissociated physiological and clinical data. In addition, many of the psychological approaches that are used are not generally regarded as stable or acceptable, by different

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Three of the patients referred to herein, were intensively studied physiologically by Dr. Asher Winkelstein, Dr. Franklin Hollander, Dr. David Orrenger, Dr. Henry Janowitz, Dr. David Dreiling, Dr. Milton Levy,—all of The Mount Sinai Hospital gastro-enterological clinic and laboratory.

Dr. M. Ralph Kaufman, Chief of the Psychiatric Service at The Mount Sinai Hospital, gave generously of his counsel and experience. The author's sincere appreciation is herewith acknowledged.

² From the Psychiatric Service of The Mount Sinai Hospital.

³ President of the American Psychosomatic Society.

investigators working with the same material. For example, a female patient whom we studied for over three years at Mount Sinai Hospital, had been previously investigated in another institution (8). Their data were regarded as significant in that the obtained results were diametrically opposed to those of the famous male patient observed by Wolf and Wolff (6). We, in our research on her, saw both kinds of responses (7). It is difficult to reconcile such apparent variability of reports on different subjects and on the same subject by different investigators. It should be pointed out that the crucial difference in all these studies probably lies in the psychological frame of reference that was used. I shall try to make this point clearer later this evening.

I shall not attempt a systematic historical review of this highly specialized type of physiological investigation based on fistulous patients. We must not forget that such research is but one, and not necessarily the best, approach to the study of gastro-intestinal physiology, and that its findings must be confirmed by other methods.

Let us digress to consider some aspects of the problem of examining the stomach by means of X-ray, test meals and the reaction to pharmacological agents such as histamine, acetylcholine derivatives and insulin. In general, X-rays and intubation techniques tend to be reliable when fixed anatomic pathology such as ulcer or neoplasm or atrophy is present. Functional disturbances without tissue changes as manifested by secretory or motility fluctuations are not always readily correlated by these methods with symptomatology in health and disease. It has been amply demonstrated that gastric activity reacts to an innumerable variety of interacting internal and external stimuli which have both inhibitory and excitatory affects (9, 10). In fact, it is a wonder that any consistency at all can be obtained. It is most likely that the pathophysiology of ulcer, neoplasm or pernicious anemia is due to the fact that these conditions constitute such overwhelming stimuli to the stomach that the influence of simultaneously opposing forces evoked by test procedures, are negligible in their effect.

It is the pathophysiology without fixed pathology of the stomach and the rest of the gastro-intestinal tract that requires elucidation. The difficulty lies in eliminating or controlling by systematic experiment the mass of variables which affect this organ system. *In vitro* experiments furnish information on the extremes of selected functional responses which are valid as empirical observations on an isolated tissue, but which cannot be applied always to an intact living organism. Such data contribute to our knowledge of general physiology, in such ways as proving that the secretory and muscular reactions of the stomach obey the principles underlying excitable tissues. It is by analogy or extrapolation that research of this kind throws light on the subtle interacting *in vivo* processes. Animal experiments, aside from the usual difficulty of generalizing the conclusions for humans, suffer because of the inability to assess psychologic factors which are undoubtedly operating in the species of animal under observation. Again, the data is valid only under extreme psychological stresses, which by anthropomorphic reasoning we attempt to extend to human subjects. For

example, in dogs with pancreatic fistuli, it was noted that when such a male dog was angered by being denied access to a bitch in heat, the freely flowing secretion stopped but resumed readily after sexual gratification (11). Similarly, another animal ceased secreting when provoked by the sight (or is it smell?) of an inaccessible cat. A different dog with a biliary fistula, observing the dissection of another animal, became intensely excited and the flow of bile was completely inhibited. These situations have in common intense psychomotor reactions in the dogs, associated with an affect which was that of excitement, rage or anxiety.

In such experiments it is clear that functional changes occur in relation to the stimuli associated with the observation. However, a chain of reactions is set into motion, which singly or in combination may account for the physiological changes. I do not believe that the stimulus *per se* is this specific effective factor. After all, the stimuli are infinite in variety and intensity, whereas the secretory and motor changes are either increased, decreased and perhaps changed as to content. At any rate, we have the problem of correlating an infinite variety of factors with at best a very few reactions. From observations on human beings, it is probable that the stimuli excite the psychophysiological complexes which are called emotions. When the stimulus is very intense, and the responding emotion drives for uncontrolled discharge, we are unable to note the influence of other interacting affects and their quantitative changes. For example, what happens to a dog's secretion if, instead of seeing a bitch in heat or of surprising a cat, it reminisces quietly about such experiences? This question is a humorous absurdity in our present state of knowledge, but it does point up the necessity for studying human beings by means of techniques which attempt to control psychologic factors.

The word "control" is meaningless in this sense, and does not apply in the kind of psychophysiologic experiments which we are discussing. If it were possible to control human emotions in any simple way, the problem of treating mental disease would not exist. The fact is that it is only the manifestations of certain emotions which can be suppressed by an act of will. Even here, the autonomic concomitants usually are affected. These may be exaggeratedly inhibited or excited by the need to avoid external expression of the emotion. That is, the physiologic state is the resultant of several emotions each acting as a vector which differs from each other quantitatively and in the direction of its expression. It is as though we were observing and hearing a symphony orchestra play as we sat in a series of different places of the concert hall. In each place we hear and see different aspects of the performance. Sometimes we are aware only of integration, a harmonious blending of different sonorities and the rhythmic motor movements of the conductor and musicians. Then we differentiate, hearing the horns while the strings are being inaudibly bowed. Or we are impressed by the contretemps of the conductor's rhythmic gestures with those of the tympanists and other players.

It is precisely this process of selective integration and differentiation in relation to our point of view that determines the kind of data we get in psycho-

physiological research. All the observations made by means of different points of view are valid, but they cannot necessarily be verified unless we can identify the integrating and differentiating processes in the observer and his position with respect to the phenomena he is observing.

It would seem, therefore, that psychophysiological research is dependent on a technique by means of which we can observe psychological events in the subject without interfering with them, while at the same time analyzing these data in terms of their variations and transformations. Thus far, in my opinion, psychoanalytic psychology comes closest methodologically to fulfilling these requirements. This view, however, does not justify the rejection of psychophysiological data obtained without reference to the psychoanalytic unconscious and defense mechanisms. On the contrary, it should be emphasized that different experiments utilizing different instruments are involved. The essential problem is to devise a field theory which would incorporate these verifiable but as yet dissociated findings.

To return to our topic of fistulae, it is correctly argued that such patients, especially with openings into the stomach and colon, are in a sense pathological subjects (12). The degree of their abnormality can be naively illustrated by asking to identify ourselves with a human being who is deprived of the major pleasure of eating by mouth and who maintains life by pouring nutriments into an abdominal opening. In the same spirit, consider the patient with an ileostomy or colostomy who cannot defecate *per anum* and who must wear a bag over the "new" bodily orifice. The people with gastric fistuli keep their lesions secret, lead much of their lives in the seclusion of their families and avoid the immensely important social experience of sharing their bread and salt. That they are subject to severe psychic stresses, our own empathy tells us. Yet, as you will see, in a paradoxical and in a remarkable way they find certain compensations which are difficult for us to conceive unless we trace the step by step process through which these psychological transformations are accomplished. I shall attempt to do this tonight.

It will be necessary first to justify the special use of the term "psychophysiology" in this paper, which may seem to some of you as an eccentric essay in psychology by me. My purpose is to present for your consideration a new research methodology in psychosomatic medicine.

The term psychophysiology achieved a definitive meaning during the last century when the German experimental psychologist Wundt (13) established a laboratory for the study of mental processes which were based on perception of external stimuli. It was not only necessary to describe what happened to a subject, but also to define as accurately as possible the precise nature of the stimulus which preceded the response. An effort was made to formulate what seemed psychological in these experiments in the same terms in which the stimuli were defined. Since only certain parts of the psychological process could be represented in this way, there developed a trend to deal only with these fragments. In short, the field of psychosensory physiology evolved in which the sense organs were studied in detail. The names of Weber, Fechner, Müller, Helmholtz, and Brücke

exemplify this form of psychophysical research at that time. The contemporary field of psychosensory biophysics as represented by Hecht, Boring, Knudsen, Crozier and others, is in part historically determined by this origin. The mental processes beyond the sensory receptor organ were not systematically correlated with psychosensory physiology, since they could not be analyzed by the same criteria. This physicalist approach began to lose sight of the fact that man had emotions which were stimulated by the activities of the sense organs. It is probably correct to say that this trend has been dramatically changed as a consequence of the psychological contributions of Freud. This development was paralleled in clinical medicine by an emphasis on organ systems in favor of the more comprehensive approach that is evolving today.

That this correlation must be made for psychophysiology is shown by the fact that every psychologist who studies the deeper aspects of his subject is obliged to hypothesize the mechanisms by which the afferent impulses from a sense organ influence the form and function of the mental apparatus. It is interesting to realize that Freud's scientific youth was spent in this atmosphere of biophysically charged research. It had a profound influence on the content and terminology of his subsequent psychoanalytic formulations.

It could be stated that Pavlov attempted the most comprehensive analysis of the problems in this field. He not only studied the sensory organ by means of conditional stimuli, but also the central nervous system and the effector end organ by means of his conditional reflex technique. When in the last few years of his life, Pavlov became interested in the psychopathology of human beings, he stopped his method of experimental verification and applied in a speculative way his findings from animals (14). There is still an enormous distance between his animal observations and the data obtained from human beings. Systematic application of Pavlovian techniques have not been applied to human beings and, as far as I know, therapies have not been derived which satisfy the rigorous criteria set up by Pavlov. Recently, Horsley-Gantt, the American leader in this field, has been investigating the autonomic nervous system by these methods (15). In the Soviet Union, there are reports which indicate that reflexologic methods are used in the investigation of mental processes such as symbolisms (16).

Recently, with the revival of the "organic approach" in psychiatry, extensive studies of metabolism and of the endocrine products have been performed, notably by Pincus, Hoagland and their groups (17). The work of Selye on the "adaptation syndrome" complemented by the use of cortisone and ACTH in a variety of psychosomatic conditions, opens a whole promising area (18). No conclusions, however, can be drawn from the reports that have been published.

Another highly complex and potential psychophysiological method has come from the neurophysiologists and neurosurgeons. The work of Penfield (19), of MacLean (20), and of Bateman and Papez (21) has been integrated by Kubie (22) into a provocative synthesis of neurophysiological and psychoanalytic concepts. Experimental developments of this theory, however, are still rudimentary.

Probably the most widely used psychophysiological methodology is that based on the pragmatic psychobiological system of Adolf Meyer. Wolf and Wolff have applied this in their extensive studies on the stomach, the colon, the nose, and vascular responses to mention a few areas.

Finally, the methodology based on psychoanalysis has been applied in two ways. The first is represented by Felix Deutsch, H. Flanders Dunbar, Franz Alexander, and Carl Binger, among many others. They tend to associate some degree of specificity of psychological and characterological factors in relation to the bodily disease. The second has been propounded by investigators, among whom are Roy Grinker, I. Arthur Mirsky, M. Ralph Kaufman, and myself. This group cannot confirm the specificity concepts (whether of character, defense or conflict) and tend to view psychosomatic illness as a group of unclassified syndromes rather than as clinical entities. Hence their research has been concerned with functions of organs in relation to psychological processes rather than with arbitrarily designated diseases.

All of these approaches, however, while radically different as to physiological methods and as to the psychological frame of reference, have been enormously fruitful. Notable contributions have been made in the accumulation of data and in the development of techniques. It should be stressed that a valid synthesis of these dissociated empirical observations and techniques, still remains to be made. The major difficulty in accomplishing this, arises from a lack of agreement as to how this should be done and as to what psychological disciplines should be used. A systematic psychology which can be accepted by everyone, does not exist as yet. The principles of theory and practice of the various schools of psychiatry cannot be translated into each others' terms. As a result, empirical observations tend to become restricted to the methodology by which they were made. As Kaufman (23), among others has shown, psychoanalytic psychology does, however, occasionally permit the data obtained by other methods, to be structured in terms of its theories and constructs.

Probably the major contribution of psychoanalysis to this area of research lies in the application of the concept of the psychological unconscious. Pavlovian reflexology, along with Penfield's formulation of the centrencephalic brain and MacLean's concept of the "visceral brain", come close to defining the anatomical localization of certain aspects of unconscious processes. These neurophysiological views cannot integrate the psychoanalytic unconscious, whereas psychoanalysis readily accommodates these anatomical conceptions (cf. Kubie).

Over the past five years the psychiatric service at Mount Sinai Hospital, in collaboration with Dr. Winklestein and Dr. Hollander of the Gastro-enterology Clinic and Laboratory, has been conducting research on the reciprocal influence of the psychological unconscious on the functional changes in gastro-intestinal viscera. We have studied a group of patients with fistulous openings into the abdominal viscera. One advantage of using such subjects is that access was provided to organs which in the intact subject, would have required extensive and possibly traumatizing instrumentation. The psychological reaction to the instrumental methods of obtaining physiological data, such as intubation, affects

the obtained data in an uncontrolled way. Various methods have been used to deal with this problem when it was appreciated. For the most part, these were directed towards the control of the psychological factor. By means of hypnosis it was assumed that the subject's perceptions of the investigative physiological procedure was changed or obliterated (24). For example, a subject in a hypnotic trance could be made to be unaware of pain, foreign bodies or the manipulations of the experimenter (25). Or, suggestions could be directed towards intensifying certain stimuli so that the summation effect of inadvertent ones would be minimized. This type of experiment was used extensively in the investigation of the psychic phases of gastric secretion (26) and in studies of biliary and pancreatic function (27). The difficulty with the hypnotic approach is that the nature of the hypnotic process and state is still unknown and hence the validity of the assumption that psychic factors have been controlled in a given way, remains to be demonstrated (28). Conditional stimuli and reflex techniques intensify certain variables in the experimental situation in such a way as to dominate and overwhelm the influence of other stimuli so that the selected variables operate as the major factors (29).

Fistulous openings allow direct visualization and manipulation of an organ, while permitting continuous psychological observation of the patient. The effects of the methods of collecting physiological data as well as the psychological significance of the fistula itself are still present. However, it is precisely the fact that the psychological factor can be expressed in all its aspects and is not tampered with as by hypnosis, conditioned stimuli or contrived experimental situations, that furnishes the most essential contribution.

It should be stressed that all examination situations are pathological ones as far as the healthy or ill subject is concerned. This induced disturbance may be compounded by the presence of a fixed disease such as a fistula and the condition which gave rise to it. For example, a patient with ulcerative colitis still retains the pathophysiology of this disease even when an ileostomy is performed. Hence two categories of data are obtained on patients with fistulous openings. The first is very well illustrated by Beaumont (4), Carlson (5), Wolf and Wolff (6), and the work done at Mount Sinai by Hollander, Kaufman, Winklestein and myself (7a). Here we see the alterations in bodily function in anatomically abnormal individuals in relation to highly selective psychological events. The second class of data has not been too well described, but it has to do with the psychological significance of the fistula itself. This problem has particularly concerned us here at Mount Sinai Hospital because of the objective fact that a subject with a fistula is in an abnormal state, and that this circumstance of itself can affect the data in an uncontrolled way. As a result, we have made extensive observations first on what the fistula does to the mental life of its possessor, and secondly how these reactions influence the bodily activities. I shall dwell on these issues with a greater emphasis on the reaction of the patient to his lesion.

The application of the concept of abnormality to fistula patients is justified by considerations other than that of the presence of an induced lesion. After all,

the organ into which an opening is made, generally has a history of disease. In other words, a bodily function has been previously dramatized by disturbances which brought the patient to a physician. This is illustrated by such conditions as ulcerative colitis, diverticulitis, regional ileitis, or genito-urinary disease. Even when the fistula is a consequence of the suicidal ingestion of a corrosive poison which seals off the esophagus, we are obliged to ask why did our patient select an oral method of self-destruction. In such situations we generally find that these patients have an exaggerated emotional investment in the sensations and functions of the mouth and upper gastro-intestinal tract (7). Hence, to the extent that such factors as I have just described are present, we are dealing with exceptional circumstances which can be regarded as deviations from a norm. The rare exception is a traumatic fistula.

As a rule, one aftermath of a surgically produced fistula is a profound change in the patient's conditioned and established biological activity. This also has far-reaching repercussions in his social and emotional life. Physiologically, the fistula deprives the patient of a given bodily function and substitutes another one usually without precedent in the patient's experience or fantasy. For example, a gastrostomy generally means that the patient may not eat by mouth. An ileostomy or colostomy similarly indicates that defecation by the anus cannot occur. Similarly, when as a result of urological surgery, urination through the urethra cannot occur, the patient both loses a function and must adapt to a new one.

There are certain common features in these diverse conditions. The mouth, anal and urethral openings are all structures at which mucous membranes meet the skin. Secondly, they are all organs which are used to discharge both bodily and psychological tensions. That the mouth serves this purpose is obvious. Concerning the anus and defecation, our literature, slang and unguarded language show beyond a doubt that these are literally and symbolically used in the emotional life of human beings. Thirdly, they all have more than one function. The mouth is not only associated with the ingestion and savoring of food, but also with speech, respiration and aggression (by vituperation, biting and spitting). It is a means of sexual pleasure through kissing and other sucking and tactile activities. One special feature of the activities of the mouth is that many of these are culturally acceptable and freely indulged publicly. It is of significance, however, that certain individuals cannot eat, speak or kiss in public. They act as though for them, these functions have some forbidden meaning with which the most painful embarrassment is associated. Descriptively speaking, they behave as if the mouth functions should be enjoyed in the kind of seclusion that is socially assigned to the toilet or bedroom.

The genitals show this multiplicity of functions in a decisive way. Aside from the fact that they are used for sexual pleasure as well as for procreation, the penis serves urination. In women, the situation is somewhat complicated in many ways. A common fantasy of function in little girls is that they too can and should stand up to urinate. When they get older and accept a more comfortable and efficient position for this function, there is more or less confusion as to the

location of the urinary meatus. The girl has to learn it. Of interest is the fact that many esthetic attitudes are fused with these organs which have to do with odors, exposure, secrecy, furtiveness, modes of dressing and undressing and modesty in general.

The anus and its function of defecation has the greatest degree of prohibition against pleasure from it. Cleanliness, punctuality, predictable regularity, and personal hygiene are among the multitude of defensive attitudes which develop. Despite our Victorian injunctions against conscious pleasure associated with the anus apart from defecation, there is no doubt about the ways in which we use the anus as a means of discharging many tensions other than those of a distended colon. As you know, the subjective sensation of pleasure does follow the relief of tension or a state of dissatisfaction.

Moreover, when for example, a lack of gratification follows intercourse, it is not uncommon for the dissatisfied individual to make up the deficit by raiding the icebox. In other words, the means of obtaining a state of gratification, i.e., relief of tension, can be displaced from one organ to the other or distributed among them. It is as though states of tension were undifferentiated and could be discharged in many different ways. This mechanism of substitution and displacement plays a prominent part in the patient's attitude towards a fistulous opening.

I should like to present a number of typical reactions and behavioral adjustments in three groups of patients with fistulous openings. Gastrostomies, ileostomies, and colostomies seem to provoke certain attitudes with common features. On the other hand, patients with tracts leading to secretory organs such as the biliary system or the pancreas appear to react differently. The third group, which consists of fistulous sinuses secondary to inflammatory disease such as occurs in perforating lesions of regional ileitis, experience severe systemic reactions and are chronically ill. They should be sharply distinguished from patients who have been restored to systemic well-being by surgery. I have no experience with patients whose openings are secondary to injuries such as bullet or stab wounds.

One patient whom I have observed for sixteen years is unique for several reasons. Due to an early diagnosis of carcinoma of the esophagus, and brilliant surgery by Dr. John H. Garlock, she was cured of the tumor. Her esophagus was resected, and a gastrostomy and an esophagostomy were performed. As a result, it was possible to study both her gastric and salivary physiology simultaneously. The esophagectomy resulted in what appears to be a total vagotomy and hence her gastric physiology would be representative of that post-operative state. The opening into her esophagus permitted certain observations on the influence of the method of collecting specimens on salivary flow. As you know, saliva ordinarily must be obtained either by aspiration or expectoration. Both methods compel the subject to avoid swallowing, i.e., to inhibit both conditional and unconditional reflexes by keeping the saliva in front of the mouth. One method involves placing an aspirating instrument into the mouth, thus furnishing a foreign body which of itself affects salivation. The other method compels the patient to expectorate the samples of saliva.

This particular patient took pride in her sense of propriety. Only the most proper and careful speech escaped her lips. She was a shy, retiring woman with great physical modesty, meticulous in her personal hygiene, and avoiding all forms of ostentation. She was moralistic and judgmental, in short, a compulsive character with whom all matters had to be just so. The physical act of expectoration was so repugnant as to be almost impossible for her. She could produce saliva by this method only when I was not present. Yet the flow from the fistulous opening into her esophagus would be copious while I was observing her. This patient's reaction is cited to demonstrate the secretory and psychic interaction which markedly affects the bodily function. Expectoration was equated by her with villification and fecal soiling, an impulse against which she reacted with an intensity amounting to violence.

Her attitude toward the two fistulous openings was of considerable interest in the light of her character makeup. She permitted only two physicians to take care of her, the surgeon and myself. When she was attended by Dr. Garlock she was cheerful; the dressings were fresh and dry and she spoke optimistically and with fortitude of the success of his operation and how well the artificial esophagus connecting the two openings was functioning. When I would see her, however, the gastrostomy and esophagostomy would be leaking, the dressings wet and malodorous with unremoved secretion and food particles. She would invariably be using worn-out tubes and pressure sponges which had been carelessly fitted. She would be disconsolate, depressed, and would ask questions concerning her routine care which had been answered previously to her satisfaction. I would clean her up, apply a fresh apparatus and either give her a glass of milk to drink or we would eat together. For me, she was the epitome of the unhappy, soiled, incontinent child. She would brighten happily as I "changed" her. Only for me and only in connection with these new bodily openings would there emerge the untidy behavior against which her whole personality was organized.

She demonstrated a striking example of regression in that she caused these orifices to function like the excretory organs of an infant, in order that she would be fondled, cleaned up, dried and fed. There was much psychological material to indicate that this situation gave her great gratification. I might add that she was addicted to cathartics and enemas. One special service which I rendered was the insertion of tubes lubricated with jelly by means of which the openings were irrigated and, so to speak, purged. She preferred to use awkward diaper pins instead of a much more efficient system of hooks and snaps.

At first, this intelligent and resourceful woman's inability to manage the essentially simple equipment which permitted her to eat normally and to avoid seclusion, was incomprehensible. She suffered physically in that she lost weight, developed hypoproteinemia and chronic avitaminosis. It was not until the psychological meaning of these openings became clear; namely, that she did not wish to be "trained," that her regression was tolerated and even encouraged. She improved rapidly. It was apparent that Dr. Garlock was a father figure to whom she re-enacted her relationship with her own father, a demanding authoritarian man to whom she was submissive and whom she always attempted to please.

I, on the other other hand, because of our intimate conversations and my continuous interest and care, became unconsciously equated to her mother with the resulting behavior towards me which I have described. Because of these deep-seated psychological mechanisms, this patient was able to transform what was a calamity into a secret form of gratification, by way of her regressive infantile behavior. Her family and friends who knew of her condition, were baffled and amazed by her seeming sense of well-being and contentment at what they regarded as a horrifying, freakish state.

Another patient, a man, exhibited a typical reaction to a colostomy performed by Dr. Garlock for ulcerative colitis. Our psychophysiological investigation was done in collaboration with Dr. William Grace of New York Hospital. The results were included in the book on the colon written by Grace, Wolff and Wolf (30). He was an executive of a large agency whose affairs he directed. In his business he was a severe and somewhat querulous task master. He had built up a large organization from which he had compelled complete loyalty and obedience, while at the same time acting with a kind of obsequious servility in relation to executives from the parent organization. In his home he was a mildly dominated husband married to a righteous, compulsive wife. He led a generally withdrawn existence, and devoted most of his attention to his business and to puttering around his suburban home. He had few significant social interests and generally prided himself upon his self-sufficiency and his security. Immediately following the institution of his colostomy, he felt himself more severely invalidated than he had been by the serious colitis that had led to this event. He could not wait for the next surgical stage to be performed to relieve him of his terrible lesion. He was unable to return to his affairs and remained at home awaiting a call for another operation. He found himself at first incapable of taking routine care of his fistula. His wife took over this responsibility completely, and he submitted to her careful cleansing and handling. The occasional efforts he made to help himself were successful only when he was angry at his wife. After a while, the care of his colostomy was ritualized and he became aware of considerable pleasure in his wife's ministrations.

Despite the fact that it was insensitive to pain or pressure, he found himself involuntarily shielding it, according to him, very much as a man does his genitals when they are threatened. He evolved a number of affectionate names for the pulpy protruding mass and would pat it tenderly when referring to it. He gained weight, felt well and finally returned to his business with his new-found secret little friend. As the time for surgery drew near, he began to entertain the idea that perhaps it wasn't necessary; it was risky and besides he was prepared to live with his lesion.

Once, as he was lying on a bed in our laboratory while awaiting some physiological experiments to be performed on him, he overheard a member of the research group invite a visitor to inspect a "freak." The patient suppressed an outward display of emotion but the mucous membrane of the exposed colostomy was seen to flush a fiery red and minute petechial mucosal hemorrhages appeared in great profusion. In his subsequent psychoanalytic observation period this incident was related to an experience in World War I, when as a wounded

prisoner of the Germans, he expected momentarily to be executed by a German officer. His ulcerative colitis, incidentally, dated from this period. What was striking was the fact that although the patient was unaware of the reaction in his colon, he associated this experience in our laboratory with the setting in which his ulcerative colitis began.

To return to his reaction to his lesion, this man transformed an unacceptable bodily insult into an organ from which he drew considerable satisfaction both intrinsically and as a result of its relation to his wife. Of some significance is the fact that he had chosen a wife with a personality like that of his mother's. The latter was a strict judgmental woman, towards whom he was submissive and obedient. He had longed for from her precisely the kind of dependency his illness had helped him to establish on his wife. Again we see the role of psychological regression operating as an adaptive and healing process. The regression always assumes a form which the patient had experienced early in life.

The third type of fistulous opening which we have observed is the ileostomy instituted in the course of the surgical treatment of ulcerative colitis. As you know, this procedure is very often followed by remarkable physical improvement and a restoration of systemic well-being in patients whose prior course had been relentlessly downhill. It is usually followed by colectomy to eliminate infected colonic tissue and as a prophylaxis against carcinomatous alteration. It is important that the emptying of feces from the ileostomy should be intermittent rather than continuous and liquid. The latter condition rapidly results in malnutrition and disturbances in electrolyte metabolism. Some patients are fortunate in that they pass practically formed stools once or twice a day at regular periods. Others may fluctuate between the favorable semi-formed stool and a so-called diarrheal state with an associated inadequate absorption of small bowel contents. That this may be determined by psychic circumstances is illustrated in the following case of an adolescent boy.

He was referred because the ileostomy failed to function properly despite the absence of any demonstrable mechanical or anatomical defects. The surgeon, Dr. Garlock, was also impressed by a disturbed marital situation in the boy's parents to which he was reacting with a bland suppression of appropriate feelings. The patient had a great deal of abdominal pain, was often febrile and had almost continuous drainage from his ileostomy. He required hospitalization from time to time to restore his nutritional and electrolyte balance. Despite the fact that he had a well-designed ileostomy bag and accessories, he seemed unable to use the equipment in such a way as to minimize fecal odors and soiling. The fact that the bag tended to fill rapidly complicated the situation. He had failed to make the usual successful adaptation to his new bodily orifice and appeared to get none of the varieties of unconscious gratification from it that had been noted in other patients. In fact, he seemed impatient with the lesion and at best indifferent and untidy about it. He had gotten the idea that he was merely marking time until the ileostomy would be taken down and attached to his colon. He also knew, however, that this was the uncommon eventuality and that in most patients the ileostomy tended to be permanent.

In the course of observation and psychoanalysis during the past four years,

it became apparent that his major concern was not the fact of the ileostomy, but the probability that his colon and rectum would be removed. His passionate desire for the anastomosis was based on the knowledge that this procedure would guarantee the preservation of his anus and rectum. It further developed that these structures had acquired a profound erotic significance for him and were involved in his masturbatory practices. This sexual investment was so firmly fixed that it was incapable of the spontaneous displacement onto the ileostomy. The details of the therapeutic steps necessary to resolve this infantile fixation would occupy the time assigned for this lecture. I shall, however, discuss the nature of analogous psychosexual reactions to a gastrostomy in the next patient. After the therapeutic resolution of this psychosexual problem, the adaptive erotization of the ileostomy took place. He has done well since. Suffice it to say at this time, Dr. S. Mouchly Small and I have collected out of a large series of patients with ulcerative colitis, a small group in whom a relapse was regularly associated with the fantasy or practice of erotic anal penetration. This phenomenon is not to be generalized for all patients with this disease. Such observations indicate the complexity and the decisive influence of deep seated psychosexual and psychophysiological factors.

Many of you may recall an elaborate investigation at this hospital of a young woman with a gastric fistula, which extended over a period of three and a half years. Members of the gastroenterological clinic and laboratory and of the psychiatric service collaborated in this research. She had occluded her esophagus as a result of a suicidal attempt with caustic lye. The detailed physiological examinations and experiments involved much instrumentation and manual manipulation by the physiologists. A good deal of recording and aspirating equipment was generally inserted into the stomach. In addition to digital palpation, it was often necessary to peer into the gastrostomy through a metal tube. There was also extensive pharmacological testing as well as experiments involving sham feeding. Throughout all this, she was under psychoanalytic observation.

This is the patient to whom I referred a little while ago in connection with the detailed psychosexual phenomena associated with a fistula into the gastrointestinal tract. The studies performed upon her have been extensively reported and those of you who may desire further amplification of our findings may refer to these publications. As I stated before in this lecture, I planned not to go into a systematic review of reported investigations.

To return to our subject, she reacted to her gastrostomy with great guilt and shame. She took elaborate precautions to avoid exposure of the fact that she had this condition. Although she resided on the psychiatric service for several years, practically none of the patients were aware of her lesion and none of the staff aside from the investigators were permitted to view her. The need to cover up her suicide attempt was not the cause of her reticence and modesty. Aside from this isolated secrecy she was a raucous, exhibitionistic, attention seeking girl.

Early in the study she cringed, wept and manifested humiliation and irritability while the physiologist went about making his observations. In her psycho-

analysis several pertinent psychological facts emerged. The first was that during the routine cleaning, rubbing and dressing of her gastrostomy, she often lapsed into pleasurable reveries whose content she invariably forgot. When these were recovered during treatment, they turned out to be vague fantasies with strong sexual coloring, usually concerned with her own genitals. It became apparent that her gastrostomy by means of displacement had acquired an erotic significance as though it were a genital. Second, she was conscious of a conviction which she knew to be irrational, that the external female genitalia were fragile structures which she must protect against the threat of sexual penetration. As a result, her reaction to the physiologist's attentions was based on the unconscious fantasy that she was being forced to submit to an intolerable heterosexual violation. She did not want her gastrostomy (unconsciously, her genitals) handled, looked at or penetrated with instruments. Needless to say, her gastric secretory, motor and vascular responses reflected this reverberating conflict. The physiologist was totally unaware of her mental contents, nor had it occurred to him that his presence and activities had provoked any unusual reaction in the subject. Third, despite her panic at the experimental situation, the proximity of the experimenter's head to her abdomen while he peered into the fistula, aroused fleeting and rapidly repressed erotic fantasies about him.

When she finally became conscious of the way and the extent to which she had sexualized both the gastrostomy and the activities of the physiologist, she reacted violently in her psychoanalysis. In the experiment, her behavior changed dramatically. Her tense, tortured and cringing attitude disappeared and she appeared relaxed, calm and drowsy. Her anxious, wide-eyed attention to the physiologist was replaced by day dreams. These had a manifest homosexual content in which she was interested predominantly in the breasts of her female partners. Concurrently, there was a striking change in her gastric physiology. She had made a psychological flight into homosexual fantasies which were more tolerable than the anxiety provoking content of her heterosexual wishes.

The last case will illustrate another type of reaction. This is to a fistula leading to a secretory organ. Such patients are not deprived of oral, anal, or urogenital functions, and these organs are not anatomically disturbed. The erotic displacement which occurs is determined by the character of the patient and his circumstances. In a sense, he has to find his way by trial and error, very much like the infant whose mouth discovers his own thumb. For such a patient and the infant, a happy and comforting association between two parts of the body is thus established.

The patient was a middle-aged man who had never been ill. However, he was too self-conscious about his well-being. He was one of those people who make it a point to have among his friends a number of doctors who seemed to be chosen for their professional skills rather than for their sociability. He suffered an acute fulminating necrotizing pancreatitis for which an emergency laparotomy and drainage were performed. It was estimated that about two thirds of his pancreas had been destroyed. The abdominal drainage tract contracted to the diameter of a small catheter. His physicians made one attempt to remove the drain tube

and to permit the sinus to close. He soon developed obstructive symptoms which indicated that pancreatic secretion did not empty into the duodenum. The tube was reinserted with some difficulty in order to permit the fluid to drain again through his abdominal wall. He reacted to this with depression, anxiety, uncertainty, and a sense of helplessness and impotence. Since he was a trained, methodical observer, he made elaborate charts of the rates and quantities of secretion, both at the request of his interested physician and in order to inform himself whether this incontinent flow from his "insides" was decreasing. He regarded this calamity as an unacceptable blow to his self-esteem. Although he seemed to have no organic ill-effects from it, he felt soiled, contaminated and "out of control." He developed neurasthenic reactions and was partially invalidated.

He was an exceptionally successful business man who headed a very large, complex and far flung enterprise. He was dedicated to what he called a "practical point of view," by which he meant a maximum control of all variables in any situation in his family, social relationships, and business. He had no tolerance for romantic impulses or motivations which did not permit one to control his self-sufficiency or security. He admired his wife enormously and he stressed that she was the spearhead of many community and do-good activities. He respected her ability as an executive in these affairs and that she ran her home, family and social obligations with the kind of managerial efficiency that he esteemed in his own spheres.

Up to the time of the unsuccessful attempt to close the fistulous tract to the bed of his pancreas, he had been confident that the involuntary drainage would subside. He had been told that surgery of the pancreas, either in the form of removal of the remaining secreting portion or of a plastic revision of the sinus was a dangerous procedure at best. If successful, he would be rendered diabetic in one case or exposed to the danger that the new duct might undergo stenosis and that he would have pancreatitis again. All the alternatives filled him with despair. His situation was further complicated by the fact that since the trial of closing the sinus tract, the catheter had become progressively more difficult to insert. Since it had to be removed daily for cleansing, he found himself progressively filled with anticipatory dread that the time would come when the tube would fail to pass through to the pancreatic bed.

He found an unexpected comfort and support in his wife. He delegated to her the daily task of intubating the tract. He would be relaxed in bed on his back. His wife would probe with the tube until it passed through. Then she would clean him and apply the dressings and collecting flask. He began to brighten perceptibly, lost his anxiety and regained much of his confidence and self-esteem. He became able to devote more and more time to his business. He began to lose interest in being a subject in our research project.

In the meantime, his surgeon's sympathy and concern had been aroused by the patient's earlier depression and despair. He offered surgery to the patient primarily to relieve the devastating sense of bodily insult and defect of which the patient had so bitterly complained. By this time, however, the patient had established the routine with his wife and felt quite comfortable. He astonished

the surgeon by refusing surgery for the very reasons which the surgeon had previously opposed it. One could speculate as to what the unconscious gratifications were that this patient managed to achieve with his wife's collaboration, and as to what erotic function had been displaced on to the pancreatic fistula.

SUMMARY

I should like to conclude this evening's somewhat discursive essay by bringing together the essential points contained in it. A fistulous opening can be used for two specific projects in psychophysiological research, both of which have been conducted at The Mount Sinai Hospital. The first, which was not elaborated upon tonight, is based on the fact that the fistula provides direct access to an organ, thus facilitating physiological research. The fact of the fistula itself, however, profoundly influences, through psychological mechanisms, the behavior of the organ to which it leads. The dynamics of secretory, motor and vascular responses can be quantitatively studied. The second, qualitatively different project, is concerned with the effect of the fistulous opening on the internal and external adaptation of the patient as a whole. It is this phase of the problem on which I have concentrated in my lecture. Several factors serve to differentiate these orifices from other varieties of bodily lesions and deformities. First, the patient is in a state of systemic well-being. Second, they are structures in which mucous membranes are in contact with the skin of the individual. Third, these patients have been deprived of a bodily function such as eating and defecation, which is delegated to the new orifices. As a result, these patients are in the position of "discovering" their new organ very much in the way that an infant, as he grows, gradually becomes aware of the functions and gratifications inherent in the mouth, anus, and urogenital structures. Fourth, the immediate reaction of the patient is one of disability and of a profound bodily insult. The lesion is incomprehensible and seems like a foreign body. During this phase, the functions of the organ are involuntary and frequently do not serve the adaptive and homeostatic bodily processes.

The process of "discovering" or of integrating the fistula into the psychophysiological (i.e., emotional) economy of the patient involves a displacement or reactivation of an infantile attitude that once prevailed in the organ whose functions have been surgically disrupted. The function that is displaced in the series of patients we have observed, appears essentially to be an erotic or sexual one. The kind of sexuality that is evoked is autoerotic and vaguely masturbatory. It is accompanied by day dreams or fantasies which are rapidly repressed and therefore become unconscious. They can be elicited by means of the psychoanalytic technique. When this erotization of the fistula occurs, it is accompanied by a subjective and objective successful adaptation to the lesion, and an associated favorable change in its function. By analogy, we can say that the patient or the orifice has become "weaned" or "bowel trained." The genital functions are not necessarily affected by this psychosexual displacement. Many of the patients in the series have made successful marital adjustments.

The second class of patients with fistulous openings, as exemplified by the

patient with a sinus tract to the pancreatic bed, have a somewhat different problem. They do not have a fundamental, conscious and voluntary vital process interfered with. As a result, they manifest only two of the three phases exhibited by the first group of patients. They show the stage of disability and incontinence, followed by an investment of the orifice with certain infantile erotic attitudes which had been incorporated into their character makeup. The first class of patients, in addition, derives a further source of pleasure based on the functions of the organ of which he was deprived by the surgery.

In addition to these observations, I should like to stress the aspect of this research which is offered as a contribution to the principles of the theory and practice of psychosomatic medicine. This is the methodology of these investigations in which the technique of psychoanalysis has been used. By means of this psychological instrument, we have demonstrated mechanisms and processes of which the patients were unaware and therefore incapable of spontaneously describing. The psychological unconscious is a powerful agent in both mental and bodily processes, very much like the involuntary autonomic nervous system in relation to the voluntary nervous system. Moreover, the application of psychoanalysis as an investigative technique carries with it valuable therapeutic implications in that the patient's psychophysiological adaptation can be accelerated. In cases where the process is inhibited as in the patient with the ileostomy whom I described, the inhibition can be lifted and the transfer of emotional investment accomplished.

And finally, I wish to close this long open letter to Dr. Moschcowitz with the hope that he has recognized in it my personal and our collective indebtedness to him.

REFERENCES

1. MOSCHCOWITZ, ELI AND ROUDIN, MATA B.: The Association of Psychosomatic Disorders and Their Relation to Personality Types in the Same Individuals. *New York State J. Med.*, 48: 1375, 1948.
2. MARGOLIN, SYDNEY G.: Anaclitic Therapy; An Analysis of the Dynamics of Superficial Psychotherapy. Abstracted in *J. Am. Psychoanalyt. Assoc.*, 8: 170, 1952. To appear in *Psychosomatic Med.*
3. ———: Metapsychology of Organ Symptom Formation. To be published.
4. BEAUMONT, WILLIAM: Experiments and Observations on the Gastric Juice and the Physiology of Digestion. Plattsburgh, F. P. Allen, 1833.
5. CARLSON, ANTON J.: Contributions to the Physiology of the Stomach. *Am. J. Physiol.*, 31: 151, 1912.
6. WOLF, STEWART AND WOLFF, HAROLD G.: *Human Gastric Function*. New York, Oxford University Press, 1947.
- 7a) MARGOLIN, SYDNEY G.: The Behavior of the Stomach During Psychoanalysis. A Contribution to a Method of Verifying Psychoanalytic Data. *Psychoanalyt. Quart.*, 20: 349, 1951.
- b) JANOWITZ, HENRY D., HOLLANDER, FRANKLIN, ORRINGER, DAVID, LEVY, MILTON H., WINKELSTEIN, ASHER, KAUFMAN, M. RALPH, AND MARGOLIN, SYDNEY G.: A Quantitative Study of the Gastric Secretory Response to Sham Feeding in a Human Subject. *Gastroenterology*, 16: 104, 1950.
- c) MARGOLIN, SYDNEY G., ORRINGER, DAVID, KAUFMAN, M. RALPH, WINKELSTEIN, ASHER, HOLLANDER, FRANKLIN, JANOWITZ, HENRY, STEIN, AARON, AND LEVY,

- MILTON H.: Variations of Gastric Functions During Conscious and Unconscious Conflict States. *Proc. Assoc. Research Nerv. & Ment. Dis.*, 29: 656, 1950.
8. CRIDER, RUSSELL J. AND WALKER, SHEPARD M.: Physiologic Studies on the Stomach of a Woman with a Gastric Fistula. *Arch. Surg.*, 57: 1, 1948.
 9. BABKIN, B. P.: *Secretory Mechanism of the Digestive Glands*. New York, Paul B. Hoeber, Inc., 1950.
 10. IVY, A. C., GROSSMAN, M. I., BACHRACH, W. H.: *Peptic Ulcer*. Philadelphia, The Blakiston Co., 1950.
 11. OECHSLER, W.: Ueber den Einfluss der psychischen Erregung auf die Sekretion der Galle und des Pankreas. *International Beitr. z. Pathol. u. Therap. d. Ernähringastor.*, 5: 26, 1913.
 12. KUBIE, L. S.: Discussion of 7a) (above). *Psychoanalyt. Quart.*, 20: 373, 1951.
 - 13a) WUNDT, WILHELM: *Beiträge zur Theorie der Sinneswahrnehmung*. Leipzig und Heidelberg, C. F. Winter, 1862.
 - b) FLUGEL, JOHN C.: *A Hundred Years of Psychology*. London, Gerald Duckworth & Co., Ltd., 1933.
 14. PAYLOV, I. P.: *Conditioned Reflexes and Psychiatry*. Introduction by W. H. Gantt. International Publishers Co., New York, 1941.
 15. GANTT, W. HORSLEY: *A Physiological Basis for Nervous Dysfunction*. *Bull. Johns Hopkins Hosp.*, 82: 416, 1948.
 16. LONDON, IVAN D.: The Scientific Council on Problems of the Physiological Theory of Academician I. P. Pavlov. *Science*, 116: 23, 1952.
 17. PINCUS, GREGORY: Measures of Stress Responsivity in Younger and Older Men. *Assoc. Research Nerv. & Ment. Dis.*, 29: 469, 1950.
 18. SELYE, HANS, FORTIER, CLAUDE: Adaptive Reactions to Stress. *Assoc. Research Nerv. & Ment. Dis.*, 29: 3, 1950.
 19. PENFIELD, WILDER, RASMUSSEN, THEODORE: *The Cerebral Cortex of Man*. New York, The Macmillan Co., 1950.
 20. MACLEAN, PAUL G.: Psychosomatic Disease and the "Visceral Brain." *Psychosomatic Med.*, 11: 338, 1949.
 21. PAPEZ, J. W.: A Proposed Mechanism of Emotion. *Arch. Neurol. & Psychiat.*, 38: 725, 1937.
 22. KUBIE, LAWRENCE S.: Some Implications for Psychoanalysis of Modern Concepts of the Organization of the Brain. Abstracted in the *J. Am. Psychoanalyt. Assoc.*, 8: 198, 1952.
 23. KAUFMAN, M. RALPH: Factors in Psychotherapy; a Psychoanalytic Evaluation. *Psychiatric Quart.*, 15: 117, 1941.
 24. WITTKOWER, ERIK: Neue Ergebnisse über affektive Beeinflussung der Magenfunktion. *Verhandl. d. deutsch. Gesellsch. f. inn. Med.*, 43: 68, 1931.
 25. HEYER, G. R.: Psychogene Funktionsstörungen des Verdauungstraktes. In: O. SCHWARTZ: *Psychogenese und Psychotherapie Körperlicher Symptome*. Wien, Julius Springer, 1925, p. 229.
 26. LANGHEINRICH, OTTO: Psychische Einflüsse auf die Sekretionstätigkeit des Magens und des Duodenums. *München. med. Wehnschr.*, 69: 1922, p. 1527.
 27. WITTKOWER, E.: Ueber den Einfluss der Affekte auf den Gallefluss. *Klin. Wehnschr.*, 7: 2193, 1928.
 28. KUBIE, LAWRENCE S. AND MARGOLIN, SYDNEY G.: The Process of Hypnotism and the Nature of the Hypnotic State. *Am. J. Psychiat.*, 100: 611, 1944.
 29. PAYLOV, I. P.: *Lectures on Conditioned Reflexes*. New York, International Publishers, 1928, Vol. I.
 30. GRACE, WILLIAM J., WOLF, STEWART, AND WOLFF, HAROLD G.: *The Human Colon*. New York, Paul B. Hoeber, Inc., 1951.

PRIMARY CARCINOMA OF THE LUNG

A FOURTEEN YEAR SURVEY*

ARTHUR H. AUFSES, M.D.

Numerous analyses of large series of cases of primary carcinoma of the lung have been published in recent years from thoracic centers or from clinics to which patients with pulmonary diseases are referred for observation. This report from a general hospital is based upon a series of patients observed at The Mount Sinai Hospital, of New York, from 1935 through 1948, a 14 year period. As the great majority of these patients were residents of New York City and environs, and since no selection or screening of patients was made (except of those admitted to the private services for operation), this analysis offers a cross-sectional view of primary carcinoma of the lung as encountered among the general population of a large city.

The period, 1935 to 1948, was chosen because the first attempts at radical resection of pulmonary carcinoma at The Mount Sinai Hospital were made in 1935; by closing the series in 1948, a follow-up period of 4 years can be evaluated. Resections of pulmonary carcinoma were performed at The Mount Sinai Hospital before 1935 (1), but were in the nature of local excisions, usually with the aid of a tourniquet; they therefore could not be classified as definitive procedures.

The Hospital records indicate that 1161 patients were discharged with a diagnosis of primary carcinoma of the lung during these years. A study of the charts disclosed that the diagnosis could not be substantiated in 177 cases. Furthermore, 25 patients had been admitted solely for bronchoscopic examination and were not observed further, even though the specimen removed revealed carcinoma. These 202 records were excluded from this series. Of the 959 case records which comprise this analysis, the diagnosis was confirmed in 850 patients by pathologic examination; in the remaining 109, the diagnosis was substantiated by adequate clinical findings.

A paper, entitled "Cancer of the Lung. Interval and Late Results of Operation in Relation to Topography and Gross Pathology" (2), was read in 1947 before the American Association for Thoracic Surgery. That report was based upon follow-up observations of 53 patients who survived operation during the years 1935 to 1945. The records of those patients are included in this report, which concerns itself primarily with the relation of the duration of symptoms to resectability and results; the relation of the topography and microscopic pathology to the end results; the relation of the anatomic site of the tumor to its resectability and results; the outcome in patients whose disease was found accidentally or through a survey film; and, finally, the moot question of the role of lobectomy, as well as the criteria for its use, in the surgical treatment of primary carcinoma of the lung.

* From the Department of Surgery, The Mount Sinai Hospital, New York City.

AGE AND SEX

Seven hundred and five patients (73 per cent) were between the ages of 50 and 69 years. Eight hundred and six (84 per cent) were males and 153 (16 per cent) were females. It is interesting to note that of the 28 patients under 40 years of age, 10 (35 per cent) were females. Table I shows the age incidence in the various decades.

TABLE I

Age

10-19 years.....	1
20-29 years.....	2
30-39 years.....	25
40-49 years.....	173
50-59 years.....	385
60-69 years.....	320
70-79 years.....	51
80+ years.....	2
Total.....	959

Sex

Male.....	806 (84%)
Female.....	153 (16%)

Of 28 patients under 40 years of age, 10(35%) were females.

SITE OF CARCINOMA

In this series, the site of the carcinoma in the unoperated patients was determined by roentgenographic, bronchoscopic, or postmortem findings. It was not always possible to determine the exact site of origin because the tumor mass had frequently grown to such size that it had crossed fissures and invaded the main bronchus or other lobar bronchi. This was also true in some patients upon whom only an exploratory thoracotomy had been performed. In the patients operated upon, the site of the tumor was determined by the findings at exploration or in the resected specimen. As a rule, the precise site of origin could be determined in the resected specimen.

In other large series, it has been shown that the right lung is more frequently the site of primary carcinoma, and that the upper lobe of that lung is most frequently involved. Table II shows that 59 per cent of the carcinomas reported originated in the right lung, with 25 per cent in the upper lobe. The more frequent occurrence of disease at this site made for a greater number of resections of carcinomas of the upper lobe of the right lung, albeit, a smaller percentage of carcinomas thus situated were resectable as compared with tumors found elsewhere in the lungs.

It is evident, as would be anticipated, that the greater number of resectable tumors (95 per cent) were those limited to a single lobe.

FIRST SYMPTOMS

In analyzing the records, it was often difficult to determine which symptom was the first to manifest itself. In some of the case histories, a number of symptoms were recorded as having appeared simultaneously.

It was determined that cough and sputum were the initial symptoms in 369 patients; only 38 per cent of the total number. To these one might add the 61 patients who gave a history of hemoptysis as the first symptom, for it is likely

TABLE II
Resectability and results in relation to anatomic distribution

SITE	NUMBER OF PATIENTS*	PER CENT AT EACH SITE	NUMBER OF RESECTIONS	PER CENT RESECTABLE	ALIVE AND WELL OR CONSIDERED CURED	
					Number of Patients	Per cent of Resections
Right Lung						
Upper lobe.....	236	25%	45	19%	12	27%
Lower lobe.....	171	18%	40	23%	6	15%
Middle lobe.....	21	2%	5	24%	0	
Main bronchus.....	83	9%	3	4%	2	67%
Right lung †.....	49	5%	2	4%	0	
Total.....	560	59%	95	17%	20	21%
Left Lung						
Upper lobe.....	167	17%	40	24%	6	15%
Lower lobe.....	115	12%	27	23%	7	26%
Main bronchus.....	55	6%	3	6%	0	
Left lung †.....	57	6%	0		0	
Total.....	394	41%	70	18%	13	18%

* In 5 cases bilateral disease was found at postmortem examination and the site of the primary tumor could not be determined.

† Bronchial origin not identifiable.

that the dramatic occurrence of a pulmonary hemorrhage dispelled all thought of earlier cough. In addition to these 61 patients, 333 had blood streaked sputum at some time in their clinical course (Table III).

The high percentage (23 per cent) of patients whose first symptom was pain in the chest is of great significance. Persistent thoracic pain, even without pulmonary symptoms, is an indication for a roentgenographic examination.

Another important group is that of 37 patients who had no pulmonary symptoms but in whom a carcinoma of the lung was found either accidentally during observation for another disease or on a routine survey. The number of patients in this group has shown a constant yearly increase. Fifteen of the 37 were seen in 1947 and 1948, and since then there has been an annual increase in the number of pulmonary carcinomas thus discovered. This group will be analyzed later

because they comprise the one important source of good results in the surgical treatment of carcinoma of the lung.

CAUSES OF CLINICAL INOPERABILITY

Under clinical inoperability are included those patients who, for various reasons, were not operated upon (Table IV). In this category, there were 626 patients; 65 per cent of the total number. Not included are the 168 patients in whom nonresectable tumors were found at operation. These 2 groups of patients comprised 83 per cent of the entire series.

TABLE III
First symptoms

No symptoms.....	37
Cough and sputum.....	369
Pain.....	216
Weakness.....	75
Pneumonia.....	71
Hemoptysis*.....	61
Dyspnoea.....	41
Cerebral symptoms.....	34
Osseous metastases.....	18
Hoarseness.....	12
Arthropathy.....	7
Metastatic nodes.....	7
Wheezing.....	6
Superior vena cava syndrome.....	5
Total.....	959

* In addition to the 61 patients whose first symptom was hemoptysis, a history of blood streaked sputum during the course of illness was given by 333 patients.

The most common cause of clinical inoperability was the presence of distant metastases; this occurred in 239 patients. Inoperability in 76 cases was attributed to the discovery of malignant cells in the pleural fluid. Nerve paralysees, proximity of the tumor to the carina, general condition or age, and metastatic involvement of the mediastinal nodes accounted for approximately 50 cases each. Other causes of clinical inoperability are to be found in Table IV.

Standards for defining clinical inoperability changed during the years covered by this survey. Improvements in surgical techniques, availability of antibiotics and blood, and advances in postoperative care resulted in a change in the evaluation of operative indications. However, despite the increased tendency to operate, the resectability rate at operation remained fairly constant, averaging 50 per cent through the years of the survey. Although it cannot be confirmed, as figures are not yet available, it seems likely that the resectability rate at operation has risen considerably in the last few years due to the increase in the number of patients in whom the disease is detected early in routine examinations.

DIAGNOSTIC METHODS

Bronchoscopic examination was the method most frequently used to obtain a specimen for study. It was performed upon 663 patients; in 428 (65 per cent), a histologic diagnosis of carcinoma was made. When a carcinoma involving an accessible bronchus was suspected, the patient was subjected to as many as 3 bronchoscopic examinations so that a positive diagnosis could be made pre-operatively, if possible. The carina biopsy, as suggested by Rabin and Kramer, was also used. By this method, a specimen is removed close to the carina to

TABLE IV
Causes of clinical inoperability

YEAR	NUM- BER OF PA- TIENTS	DIS- TANT METAS- TASES	MALIG- NANT CELLS IN PLEU- RAL FLUID	NERVE PARALY- SES	TOO CLOSE TO CARINA	GEN- ERAL CONDI- TION OR AGE	MEDI- ASTINAL NODES ON X-RAY	CEASED SHORTLY AFTER ADMIS- SION	RE- FUSED OPERA- TION	MISCEL- LANE- OUS	TOTAL CLINI- CALLY IN- OPER- ABLE	PER CENT CLINI- CALLY INOPER- ABLE
1935	39	10	4	4	2	3	4	6	1	0	34	87%
1936	50	15	6	7	1	8	2	4	0	4	47	94%
1937	57	11	7	2	5	4	3	1	7	5	45	79%
1938	48	13	7	4	0	3	2	2	3	3	37	77%
1939	51	14	3	1	3	2	3	3	4	3	36	70%
1940	57	16	3	0	3	6	6	7	2	1	44	77%
1941	61	14	7	3	2	3	2	3	6	4	44	72%
1942	61	9	8	7	3	1	4	2	3	3	40	65%
1943	71	11	4	4	4	3	6	2	3	0	37	52%
1944	76	15	5	3	4	3	1	5	4	1	41	54%
1945	102	30	6	4	8	3	5	2	2	0	60	59%
1946	85	22	5	5	6	1	2	3	1	2	47	55%
1947	91	29	3	2	3	2	1	1	4	2	47	52%
1948	110	30	8	5	7	5	2	4	4	2	67	60%
Total	959	239	76	51	51	47	43	45	44	30	626	65%

determine the presence of carcinoma cells in the submucous lymphatics. A positive report makes exploration inadvisable. A small number of patients were thus spared an exploratory procedure.

A pathologic diagnosis was made in 62 patients by examination of a superficial node, usually supraclavicular. In 50, malignant cells were found in the pleural fluid. Lung aspiration was positive in 39 patients, and in another 34, a positive specimen removed from other metastases, usually bony, precluded operation. During the years covered by this survey, the Papanicolaou method for examination of sputum or bronchial washings was used in only a small number of instances.

DURATION OF SYMPTOMS

The delay in diagnosis and late surgical intervention in primary carcinoma of the lung have been amply discussed in the literature. It is evident that in

lung cancer, as in any malignant tumor, the earlier the diagnosis is established and operation performed, the better will be the prognosis. Table V shows the relationship of resectability and good results to the duration of symptoms. With the exception of the group who had no pulmonary symptoms but in whom the disease was found accidentally, there was no appreciable difference in either resectability or end results whether the symptoms were of short or long duration.

The resectability rate increased slightly as the duration of symptoms lengthened from less than one month to 6 months. It then dropped during the

TABLE V
Resectability and results in relation to duration of symptoms

DURATION OF SYMPTOMS	NUMBER OF PATIENTS	RESECTIONS	PER CENT RESECTABLE	ALIVE AND WELL OR CONSIDERED CURED	
				Number of Patients	Per cent of Total Number of Patients
No symptoms					
Found clinically.....	32	14	44%	5	16%
Found at post mortem.....	5	0		0	
Less than one month.....	81	8	10%	1	1%
1-2 months.....	157	19	12%	5	3%
2-3 months.....	149	24	16%	3	2%
4-6 months.....	231	50	21%	10	4%
7-12 months.....	119	18	15%	2	2%
13-24 months.....	107	18	17%	4	4%
25-36 months.....	48	10	21%	2	4%
37-48 months.....	21	3	14%	1	5%
More than 4 years.....	9	1	11%	0	
Total.....	959	165	17%	33	3.4%

7 to 24 month period, and increased again when the duration of symptoms was from 2 to 3 years. The percentage of good results apparently fluctuates in a manner similar to that of the resectability rate. The data in Table V seem paradoxical for they give the impression that the ultimate prognosis improves as the duration of symptoms is prolonged. If this were so, it could only be explained by the fact that there is a type of asymptomatic carcinoma of the lung which grows slowly and metastasizes late. Such carcinomas might tend to give good results even though operations were delayed.

The most interesting group was that of 37 patients who had no pulmonary symptoms but in whom the disease was found during examination for non-pulmonary complaints, on routine or survey examinations, or at post mortem. The disease was discovered in 21 instances through a routine or survey examination; in 4, at fluoroscopy during a gastrointestinal series; in 3, on a chest roentgenogram during examination for genitourinary symptoms; and in one, during

the course of a coronary occlusion; one patient was under observation for chronic pulmonary tuberculosis; another for diabetic acidosis; and still another for a chest injury. The remaining 5 patients in this group died from other causes and carcinoma of the lung was revealed at postmortem examination. The diagnosis was established in 15 of these 37 patients during 1947 and 1948.

It is encouraging to compare the course of the 15 patients without symptoms whose disease was discovered in 1947 and 1948 with the 17 in the earlier years.

	1935-1946	1947-1948
Clinically inoperable when discovered.....	8	2
Refused operation.....	1	2
Inoperable at exploratory thoracotomy.....	3	2
Resectable.....	5	9
	—	—
	17	15
Alive and well.....	1	4

In the group seen before 1947, even though pulmonary disease was found on a roentgenogram, many of the patients were followed for many months or even years before a diagnosis of carcinoma was made. The small number of resectable tumors and the good result in but one patient is a sad commentary on the attitude toward asymptomatic pulmonary abnormalities in those years. The much higher resectability rate and number of good results in the years 1947 and 1948 is evidence of an increasing tendency to earlier exploratory thoracotomy for undiagnosed pulmonary disease. The significant decrease in surgical mortality has undoubtedly been a factor in accelerating this trend.

MICROSCOPIC PATHOLOGY

A pathologic diagnosis of carcinoma was made in 850 patients, but the exact type of cell could not be determined in 140. Most of the latter were those in whom the malignancy was diagnosed from pleural fluid cytology or from aspirated tissue. The types of cells found in the 710 patients are listed in Table VI. It is evident that almost one half of the carcinomas of the lung were the squamous cell type, with anaplastic carcinoma and adenocarcinoma each comprising one-fifth of the total number.

The cases in which the type of cell could be identified, and an analysis of the resectability of each type are listed in Table VI. As to resectability, it was found that 30 per cent of the squamous cell carcinomas were resectable, 23 per cent of the adenocarcinomas, 15 per cent of the anaplastic carcinomas, and only 5 per cent of the small cell group.

Of the 160 resections in which the cell type could be determined, 102 (64 per cent) were squamous cell carcinomas, 20 per cent were adenocarcinomas, 13 per cent were anaplastic carcinomas, and 2.5 per cent were small cell carcinomas (Table VI).

These cases have been studied not only according to microscopic pathology, but also according to their clinical and topographic features, as originally described by Neuhof, Rabin and Sarot (3), using 3 groupings: (a) main bronchus

cancers; (b) circumscribed peripheral cancers; and (c) peripherally invasive cancers.

In the first group, main bronchus cancers, are included those tumors originating in one of the larger bronchi (main bronchus or main lobar bronchus). They are usually characterized by early bronchial symptoms, are practically always accessible to the bronchoscopist, and have a tendency to extend early to the hilar and mediastinal lymph nodes by lymphatic spread. Under the second grouping, circumscribed peripheral tumors, are classified those which appear as rounded or slightly lobulated shadows in the roentgenogram. They are usually situated some distance from the hilum and are frequently asymptomatic. They arise from a small bronchus or bronchiole and are seen bronchoscopically only

TABLE VI
Resectability in relation to microscopic pathology

MICROSCOPIC PATHOLOGY	NUMBER OF PATIENTS*	RESECTIONS	PER CENT RESECTABLE
Squamous cell carcinoma.....	339	102	30%
Anaplastic carcinoma.....	146	22	15%
Adenocarcinoma.....	141	32	23%
Small cell carcinoma.....	78	4	5%
Carcinoma simplex.....	6	0	
Total.....	710	160	

* A pathologic diagnosis of carcinoma was made in 850 patients, but the type of cell could be determined in only 710.

when they have grown large enough to erode a main or lobar bronchus. They may grow to large size before causing symptoms, and they have a tendency to spread hematogenously rather than through the lymphatics.

The third group, the peripherally invasive type, includes those tumors which arise from small bronchi in the periphery of the lung and invade the surrounding tissues, such as the chest wall, diaphragm, pericardium, vertebral column, or the brachial plexus. Their lymphatic spread appears to be outward into surrounding tissues rather than toward the hilum.

The relationship of the microscopic pathology to the topographic classification is also of interest (Table VII). Only in the resected specimens could this be determined with a fair degree of accuracy. It is quite evident that a high percentage of squamous cell carcinomas can be found in both the main bronchus tumors and the peripherally invasive tumors. The circumscribed tumors include a relatively high percentage of adenocarcinomas.

We believe that this topographic classification is an aid in determining both the type of operation which may be indicated and the prognosis.

EXPLORATORY THORACOTOMY

We deem an exploratory thoracotomy a procedure with very little morbidity or mortality; we are of the opinion that it should be performed when there is

no definite evidence of distant metastases or extensive extrapulmonary intrathoracic spread. Of the 333 patients who were operated upon, 168 were found to have tumors which were nonresectable. Inability to perform a resection was due to direct invasion of the hilum with extension into the mediastinum, inva-

TABLE VII
Results in relation to topography and microscopic pathology

TOPOGRAPHY	RESECTIONS*	OPERATIVE SURVIVALS	ALIVE AND WELL OR CONSIDERED CURED		
			Number of Patients	Per cent of Resections	Per cent of Operative Survivals
Squamous Cell Carcinoma					
Main bronchus†.....	60	37	13	22%	35%
Circumscribed.....	27	20	6	22%	30%
Peripheral invasive.....	15	10	2	13%	20%
Total.....	102	67	21	20%	31%
Adenocarcinoma					
Main bronchus†.....	6	3	0		
Circumscribed.....	23	16	10	44%	62%
Peripheral invasive.....	3	2	0		
Total.....	32	21	10	31%	48%
Anaplastic Carcinoma					
Main bronchus†.....	13	8	0		
Circumscribed.....	6	2	1	16%	50%
Peripheral invasive.....	3	2	1	33%	50%
Total.....	22	12	2	9%	17%
Small Cell Carcinoma					
Main bronchus†.....	4	4	0		
Circumscribed.....	0	0	0		
Peripheral invasive.....	0	0	0		
Total.....	4	4	0		

* Five cases not classified as to topography and pathology have been omitted.

† Includes main lobar bronchi.

sion of the vertebral column, or very extensive invasion of the diaphragm or thoracic wall. In the years covered by this report, mediastinal dissection was not performed, consequently, in those patients who had extensive mediastinal lymph node involvement, resection was not performed. Of the 168 patients found to have nonresectable tumors, 21 (12.5 per cent) died postoperatively. Most of these deaths occurred in the early years of the study. During the final

three years of this study (1946-1948), 63 exploratory thoracotomies were performed with only 3 postoperative deaths, a mortality of 4.8 per cent (Table VIII). The fact that these patients were suffering from extensive malignant disease and many of them were in the older age groups would stress the relative safety of an exploratory procedure.

TABLE VIII
Primary carcinoma of the lung, 1935-1948

YEAR	NUMBER OF PATIENTS	CLINI- CALLY INOPER- ABLE	INOPER- ABLE AT OPERA- TION	PER CENT INOPER- ABLE	NUMBER RESECT- ABLE	PER CENT RESECT- ABLE	NUMBER POST- RESECT- ION DEATHS	OPERA- TIVE MORTAL- ITY	SURVIVED OPERA- TION	ALIVE AND WELL	CON- SIDERED CURED
1935	39	34	2	92%	3	8%	3	100%	0	0	0
1936	50	47	1	96%	2	4%	1	50%	1	0	0
1937	57	45	7	91%	5	9%	3	60%	2	0	0
1938	48	37	3	83%	8	17%	7	87%	1	0	0
1939	51	36	6	82%	9	18%	6	66%	3	0	2
1940	57	44	7	89%	6	11%	5	83%	1	0	0
1941	61	44	9	87%	8	13%	5	62%	3	1	1
1942	61	40	14	88%	7	12%	1	14%	6	1	0
1943	71	37	18	77%	16	23%	5	31%	11	1	0
1944	76	41	16	75%	19	25%	4	21%	15	6	1
1945	102	60	22	80%	20	20%	9	45%	11	2	0
1946	85	47	23	82%	15	18%	3	20%	12	4	1
1947	91	47	18	71%	26	29%	6	23%	20	5	2
1948	110	67	22	81%	21	19%	3	14%	18	5	1
Total	959	626	168	83%	165	17%	61	37%	104	25	8

There were 21 postoperative deaths following 168 exploratory thoracotomies (12.5%).

In the last 3 years, 1946-1948, there were 3 deaths following 63 exploratory thoracotomies (4.8%).

SURGICAL RESULTS

It is believed that a 4 year follow-up period is sufficient for accurate evaluation of the end results of operation because, as shown by Neuhof and Aufses (2), a very high percentage of recurrences, metastases, or death occur in the first 3 postoperative years. In this series, 104 patients survived operation and 33 are "alive and well or considered cured." The time of recurrence, metastasis, or death is known for the remaining 71 patients. Of these, 67 (94 per cent) were thus affected within the first 3 postoperative years (Table IX).

In order to have a follow up of 4 years and also to give an over-all picture, the worst years (from the surgical standpoint) have been included, and the best years (those since 1948) have been excluded, in this survey. Resection was performed in only 50 per cent of the operated patients and the postoperative mortality was 37 per cent (Table VIII). In view of this high mortality, "alive and well or considered cured" patients have been studied in relation to the number who survived operation as well as to the number upon whom resection was performed. It is believed that thereby a better picture of the prognosis in various types of

carcinoma of the lung is achieved. Study of the relationship of results to operative survival should also aid in anticipating the end results of current operative procedures, with their lower postoperative mortality.

From 1935 to 1948, 165 resections were performed; 112 pneumonectomies and 53 lobectomies. The belief that lobectomy can be considered an adequate operation for some types of carcinoma of the lung accounts for this large number of lobectomies. We do not hesitate to perform a lobectomy when by our criteria it is indicated, not only in poor risks, but even in those who appear to be good risks and where pneumonectomy is not contraindicated. The operative mortality in the pneumonectomy group was 40 per cent, whereas in the lobectomy group it was 30 per cent. Nineteen (17 per cent) of the 112 patients subjected to pneumonectomy are alive and well or considered cured; 14 (26 per cent) of the patients upon whom lobectomy was performed are in this category. In relation

TABLE IX
Postoperative year in which metastasis, recurrence, or death occurred

First year.....	47
Second year.....	15
Third year.....	5
Fourth year.....	3
Sixth year.....	1
Total.....	71

to the number who survived operation, 28 per cent of the "pneumonectomies" and 38 per cent of the "lobectomies" are considered as good results. These figures would tend to contradict the contention that lobectomy is a grossly inadequate operation (Table X).

In analyzing the results of surgical procedures for carcinoma of the lung in patients in the older age group, one must expect to find that some died of causes other than the original disease. To cover this contingency, we have used the classification of "alive and well or considered cured." Of 33 patients in this group, 25 are alive and well and 8 are considered cured. Of this latter number, 2, operated upon in 1939, were lost to follow up after 7 and 10 years, respectively. Six have died, but study of their histories has led to the belief that they can be classified as good results. For completeness, a brief abstract of these case histories follows:

(1) A. R., * 484193, aged 57, was operated upon November 12, 1941, for a peripheral invasive squamous cell carcinoma of the right upper lobe with involvement of the third, fourth, and fifth ribs. A right upper lobectomy was performed, with excision of the involved chest wall. A small empyema developed for which a revision operation was performed two months later. The patient was well until November, 1945, when symptoms appeared which indicated disease in the left lung. Bronchoscopic examination revealed a tumor of the left main bronchus. This was reported as an anaplastic carcinoma. Because of its situation in the contralateral main bronchus, its dissimilar microscopic pathology, and the time interval since the initial operation, it was considered to be a second primary tumor.

(2) H. T., #516181, aged 58, was operated upon February 3, 1944, for a circumscribed adenocarcinoma of the right upper lobe. A tourniquet type of lobectomy was performed, with resection of the right upper and middle lobes. He made an uneventful recovery and was perfectly well until 1948 when he died of a coronary occlusion. Postmortem examination revealed no evidence of carcinoma.

(3) J. G., #557900, aged 52, was operated upon December 21, 1946, for a squamous cell carcinoma of the lung. A pneumonectomy was performed. He was well until 1950, at which time he was readmitted because of symptoms referable to the urinary bladder. A transitional cell carcinoma of the bladder was found, and a bilateral ureterosigmoidostomy was performed. At a second operation, an unsuccessful attempt was made to perform a cystectomy. He died in March, 1951, of bilateral pyelonephritis and carcinoma of the bladder.

(4) A. N., #569470, aged 59, was operated upon August 28, 1947, for an adenocarcinoma of the left lung. A pneumonectomy was performed. Empyema developed and was drained in January, 1948. The empyema space was obliterated by subsequent procedures. He was well until February, 1952, when he developed symptoms of a brain tumor. He died in March,

TABLE X
Results in relation to operative procedures

OPERATION	RESECTIONS	OPERATIVE SURVIVALS	ALIVE AND WELL OR CONSIDERED CURED		
			Number of Patients	Per cent of Resections	Per cent of Operative Survivals
Pneumonectomy.....	112	67	19	17%	28%
Lobectomy.....	53	37	14	26%	38%
Total.....	165	104	33	20%	32%

1952. Postmortem examination revealed the brain tumor to be a spongioblastoma. No evidence was found of metastases from the original pulmonary carcinoma. (Without a postmortem examination, this case would have been classified as a death from metastatic carcinoma.)

(5) M. S., #568198, aged 70, had been operated upon in 1928 for a carcinoma of the splenic flexure of the colon for which a partial colectomy had been performed. In January, 1947, he had a subtotal gastrectomy for an adenocarcinoma of the stomach. At this time, a roentgenogram of the chest was negative. Soon after the gastrectomy, he began to cough and expectorated some blood streaked sputum. An infiltration in the right upper lobe was discovered in May, 1947, and a bronchoscopic examination in July disclosed a narrowing of the right upper lobe bronchus. Biopsy showed squamous cell carcinoma. A right pneumonectomy was performed on October 4, 1947, and he remained well until 1949, when he was readmitted on a number of occasions because of gastrointestinal hemorrhages, the source of which could not be determined. He died on May 6, 1950. Postmortem examination revealed the cause of death to be an organizing bronchopneumonia of the left lung. There was no evidence of carcinoma.

(6) C. F., #581922, aged 65, was operated upon July 3, 1948, for a squamous cell carcinoma of the left main bronchus. A pneumonectomy was performed, following which he was well for 2½ years. He died suddenly while sitting in a park.

The records of those patients upon whom a resection was performed have been analyzed from various viewpoints. Two phases have been of especial interest: (a) the relationship of the topography, microscopy, and node involve-

ment to resectability and good results and (b) the controversial question of the role of lobectomy in the surgical treatment of primary pulmonary carcinoma.

Although 165 resections were performed or attempted, complete pathologic examination was obtained in only 160 specimens. As previously mentioned, no attempt at radical mediastinal dissection was made during these years. Carcinomas that presented widespread mediastinal node involvement were generally not resected and palliative pneumonectomy was seldom performed. In some of the cases, pneumonectomy was combined with the "plucking" of involved nodes from the mediastinum. Such cases have been classified as "with involved

TABLE XI
Results in relation to topography and node involvement

TOPOGRAPHY	RESECTIONS	OPERATIVE SURVIVALS	ALIVE AND WELL OR CONSIDERED CURED		
			Number of Patients	Per cent of Resections	Per cent of Operative Survivals
With Node Involvement					
Main bronchus*	47	31	4	8%	13%
Circumscribed	15	8	0		
Peripheral invasive	1	1	0		
Total	63	40	4	6%	10%
Without Demonstrable Node Involvement					
Main bronchus*	36	21	9	25%	45%
Circumscribed	41	30	17	41%	57%
Peripheral invasive	20	13	3	15%	23%
Total	97	64	29	30%	45%

* Includes main lobar bronchi.

nodes." In the majority of resected specimens, the presence or absence of involved nodes was determined by examination of the nodes attached to the specimen; these, as a rule, were hilar nodes.

Table XI shows that the prognosis following resectional therapy is especially poor when hilar nodes are involved. There were 97 patients with no demonstrable metastatic node involvement; of these, 29 (30 per cent) are alive and well or considered cured. Of 63 patients upon whom resection was performed for carcinoma with known node involvement, only 4 (6 per cent) are alive and well or considered cured. In 2, numerous nodes were found, but only one involved node could be found in each of the others. These 4 patients, operated upon in 1944, 1945, 1946, and 1948, respectively, had squamous cell carcinomas. Table XI also shows that in patients without demonstrable node involvement, pulmonary resection gives the best results in the circumscribed type of carcinoma.

Table XII indicates the relationship of the type of operation, as well as the

topography of the tumor, to the results obtained. Lobectomy was used only in the surgical treatment of circumscribed or peripheral invasive tumors. The fact that the patients with circumscribed tumors apparently had better results with lobectomy than with pneumonectomy requires elucidation. Lobectomy was performed for small carcinomas, those limited to a single lobe and without demonstrable lymph node metastases at the time of operation. When the tumor was large, near the hilum, had evident node metastases, or crossed a fissure,

TABLE XII

Results of operative procedures in relation to topography

OPERATION	RESECTIONS*	OPERATIVE SURVIVALS	ALIVE AND WELL OR CONSIDERED CURED		
			Number of Patients	Per cent of Resections	Per cent of Operative Survivals
Main Bronchus†					
Pneumonectomy.....	79	48	13	16%	27%
Lobectomy.....	4	2	0		
Total.....	83	50	13	16%	26%
Circumscribed					
Pneumonectomy.....	28	18	6	21%	33%
Lobectomy.....	28	21	11	39%	52%
Total.....	56	39	17	30%	44%
Peripheral Invasive					
Pneumonectomy.....	2	1	0		
Lobectomy.....	19	14	3	16%	21%
Total.....	21	15	3	14%	20%

* Five cases not classified as to topography have been omitted.

† Includes main lobar bronchi.

pneumonectomy was performed. It is apparent, therefore, that under these circumstances a higher percentage of good results would be obtained with lobectomy for circumscribed tumors rather than with pneumonectomy.

It is believed that the histology of a tumor is the best guide to its potential malignancy and ultimate prognosis. Squamous cell carcinomas are considered to be the most amenable to operation and yield the best results. This is not proven by analysis of the microscopic findings in the resected specimens. Table VII shows the relationship of good results to operative survivals and resections in each of the 4 histologic groups. It is apparent that adenocarcinomas offer the best prognosis. Of 32 patients with adenocarcinoma, 10 (31 per cent) are alive and well or considered cured as compared with 20 per cent of the patients

with squamous cell carcinomas and 9 per cent of those with anaplastic carcinomas. On the other hand, these figures, when analyzed on the basis of topography, show that the good results with adenocarcinoma are due to the fact that 23 of the 32 resectable adenocarcinomas were circumscribed (Table VII). Here it is also evident that the circumscribed adenocarcinoma gives the highest percentage of good results since 44 per cent of the patients with this type of resectable tumor are alive and well or considered cured. Patients with a circumscribed carcinoma have twice the chance for cure as contrasted with those having main bronchus or peripheral invasive carcinoma (Table XII).

The comparative results of lobectomy versus pneumonectomy in the treatment of primary carcinoma of the lung are presented in Table X. These figures indicate that a lobectomy can be curative in a fair percentage of carefully selected cases.

Despite the fact that the patients subjected to lobectomy are usually considered poor risks, the mortality is less than that with pneumonectomy. That pneumonectomy is a more radical operation for carcinoma of the lung is unquestioned. Were the operative mortality, postoperative complications, and disturbance of respiratory function (at least in the ultimate survivors) the same for both types of resection, there would be no need to suggest the use of lobectomy in primary carcinoma of the lung. The lowered postoperative mortality in all types of pulmonary resections at the present time tends to lessen the difference in mortality between the two operative procedures, so that the relative difference now is not so great as it was during the years covered by this survey.

The follow up of our patients seems to indicate that the deaths were caused by distant metastases and not by intrathoracic recurrence. That many of the metastases occur so soon after operation implies that they were already present at the time of the resection or, as has been suggested (4), they might have been induced by the operative procedure. Therefore, one is prone to question whether pneumonectomy could have been curative where lobectomy had failed.

More complications follow pneumonectomy than lobectomy, and frequently they necessitate additional operative procedures and prolonged hospitalization. Although the respiratory function may be slightly diminished following lobectomy, the patients can usually return to their original occupation. With pneumonectomy, however, the respiratory function often is so poor that patients may be semi-invalided, and rarely can they resume an arduous occupation. This factor must be considered in choosing between the two procedures. The indications for lobectomy, however, must be quite clear from the pathologic standpoint in every case in which it is to be used as a definitive procedure. Lobectomy should be considered only when the roentgenogram reveals a well defined, round, or only slightly lobulated shadow. This is occasionally better demonstrated by sectional radiography. In many of these cases, bronchoscopy is of no value, but if bronchoscopic examination has been performed and the biopsy has been reported as positive, lobectomy should not be considered.

At operation, the tumor mass must be confined to one lobe which has relatively

well defined fissures and should not be in close proximity to the hilum. The hilar area should be dissected and any nodes present removed and examined by frozen section. The mediastinum should also be investigated for metastatic nodes. The presence of involved hilar or mediastinal nodes is a contraindication to lobectomy. The examination of the hilum and mediastinum in this manner may be subject to criticism because involved nodes may be missed and microscopic node involvement may not be found on frozen section. The cures in cases with hilar or mediastinal node involvement are so few that once involvement has occurred, the superior value of pneumonectomy as compared with lobectomy will be greatly lessened. We will have to await a follow-up study on those patients who have been subjected to pneumonectomy with radical mediastinal dissection to determine the percentage of cures that can be obtained thereby, when node involvement is present.

A year by year analysis of the entire series is contained in Table VIII, which shows the gradually increasing number of patients seen in the Hospital over the 14 year period. The percentage of patients found to have nonresectable tumors has varied from 96 per cent in 1936 to a low of 71 per cent in 1947, with an average of 83 per cent. It is our impression that since 1948 the percentage of resectable cases has increased considerably.

The number of good results, only 33 of the 959 patients, is indeed low; yet 20 per cent of the patients upon whom resection was possible are alive and well or considered cured in spite of an operative mortality of 37 per cent for the entire series. Of 104 patients who survived operation, 32 per cent are considered good results. Due to the improvements in surgical technique and anaesthesia, a better knowledge of pulmonary and cardiac physiology, the use of antibiotics, and all the other adjuvants to surgery, operative mortality was reduced from 100 per cent in 1935 to 14 per cent in 1948. In succeeding years, there has been a further decrease in postoperative deaths. This decrease in operative mortality will permit an increasing number of patients to have the chance for cure through surgery and thereby add to the number of long term survivors.

SUMMARY

A series of 959 cases of primary carcinoma of the lung observed at The Mount Sinai Hospital, New York, from 1935 through 1948 has been reviewed.

They have been analyzed in respect to various clinical features.

The results of surgical therapy have been determined with a follow-up period of 4 years or more.

An attempt has been made to determine the relationship of the end results to microscopic pathology, topography, node involvement, site of the carcinoma, duration of symptoms, type of operation, and absence of symptoms.

The place of lobectomy and pneumonectomy in the surgical therapy of primary carcinoma of the lung is discussed.

Acknowledgment

I wish to thank the Thoracic Surgeons of The Mount Sinai Hospital for permission to include the records of their private patients in this report and for their aid in determining the follow-up status.

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REFERENCES

1. NEUHOF, H.: The Operative Treatment of Carcinoma of the Lung. *S. Clin. North America*, 13: 363, 1933.
2. NEUHOF, H. AND AUFSES, A. H.: Cancer of the Lung. Interval and Late Results of Operation in Relation to Topography and Gross Pathology. *J. Thoracic Surg.*, 17: 297, 1948.
3. NEUHOF, H., RABIN, C. B., AND SAROT, I.: A Topographic Classification of Cancer of the Lung, with Special Reference to the Surgical Implications of the Circumscribed Variety. *J. Thoracic Surg.*, 11: 388, 1942.
4. AYLWIN, J. A.: Avoidable Vascular Spread in Resection for Bronchial Carcinoma. *Thorax*, 6: 250, 1951.

GRANULOSA CELL TUMOR*

ALEXANDER BELLWIN, M.D. AND M. A. GOLDBERGER, M.D., F.A.C.S.

In the seventeen year interval 1933-1949 inclusive, there were admitted, and operated upon, a total of nine cases of granulosa cell tumor of the ovary, on the combined ward and private services of the Mount Sinai Hospital.

The histogenesis of this tumor has been a matter of considerable speculation. Robert Meyer (1) postulated that these tumors arise from rests of redundant granulosa cells left in the ovary in the process of follicle formation. Schiller thought that the origin could be traced still earlier to ovarian mesenchyme which could differentiate into either granulosa cells or theca cells since elements of both were frequently found together in one tumor. Butterworth (2) and Geist (3) produced granulosa cell tumors in mature female mice by the use of Roentgen rays. The primary effect of X-rays is to cause destruction of cell ovocytes and degeneration of the follicles. In these experimental animals, the neoplasm appeared to spring from the degenerating follicular epithelium. Other authors have supported the contentions of Butterworth and Geist of this possible origin of granulosa cell tumors (4). The problem of possible etiology was attacked from another direction by Biskind and Biskind (5), who transplanted the ovaries of three female castrated rats into the spleen with the consequent formation of granulosa cell tumors in the grafts, the rationale being that the liver inactivates the ovarian hormones when they are circulated through the hepatic portal system and the overaction of the gonadotropic hormones secondary to castration is responsible for the development of the ovarian tumors. Using mice, Li and Gardner (6) noted two granulosa cell tumors and one "pre-tumorous" growth after the animals were castrated and either autoplasmic or homoplastic ovarian grafts to the pancreas were performed. It is of interest that with similarly treated animals, the administration of estrogens inhibited any tumor formation. Peckham, Greene and Jeffries (7) reported similar results using female rats and rabbits.

Granulosa cell tumors may vary greatly in size; from tumors a few millimeters in diameter to those which fill the entire abdomen. They usually present a smooth outer surface which is frequently lobulated, and may be solid or cystic. Areas of yellowish hue are said to be characteristic (8). On microscopic examination, these tumors show extreme variability, not only from one tumor to another, but in different areas in the same neoplasm. In general, the cells resemble granulosa cells and have growth characteristics identical with those of granulosa tissue. Granulosa cell tumors are commonly described as one of three types: the folliculoid, characterized by rosettes and small clusters with areas of liquefaction resembling the "Call-Exner" bodies so characteristic of granulosa cell growth in such animals as the rabbit; the diffuse or parenchymatous, characterized by growth in sheets of cells; and the cylindromatous, in which the epi-

* From the Department of Gynecology, The Mount Sinai Hospital, New York, N. Y.

thelial masses are split into cylinders or columns by connective tissue invasion. Any of these types may show evidence of luteinization.

The incidence of granulosa cell tumor of the ovary is variously reported as 10% of all solid malignant ovarian neoplasms (8), 2.5% of all ovarian neoplasms (9), 4% of all ovarian neoplasms (10), and 1.63% of ovarian tumors (11). At the Mount Sinai Hospital, the incidence is far lower, 0.6% of all ovarian neoplasms. According to Spencer and Hollenbeck (9), 90% of these are unilateral. In a review of their cases, Dockerty and MacCarty (12) report no cases of bilateral involvement. In our small series, two of the eight cases were bilateral.

Estimates of the malignancy of these tumors vary greatly, being reported by Meyer (1) as 10-28%; by Jones and TeLinde (13) as anywhere from 10-55%. It is difficult to evaluate this factor because of the reported cases of very late recurrence, even as long as twenty one years following surgery (13). Dockerty and his coworkers (11, 15) feel that these tumors are of low grade malignancy and somewhat radiosensitive.

These tumors may occur at any age (10, 12, 16, 17). In children they frequently cause precocious puberty with anovulatory menstruation (19, 20). In the normal reproductive adult, one may find normal menses, hypermenorrhea, or amenorrhea and frequently associated sterility (10, 21, 22, 23), although coexistent pregnancies have been reported (9). The blood estrin (24) and the urinary gonadotropic levels are frequently elevated and there may be a positive A-Z test (10, 25). In the postmenopausal woman, there may occur a "rejuvenation" with reappearance of menses. Interestingly enough, following the surgical removal of these tumors, the woman may reexperience menopausal symptoms.

A most interesting facet of granulosa cell tumors is their frequent association with endometrial hyperplasia, and not infrequent association with carcinoma of the endometrium (15, 17, 26, 27), or carcinoma elsewhere in the body.

REPORT OF CASES

Case #1: B. S., #408490, a 71 year old white widowed female was suddenly taken ill several hours prior to admission with severe right lower quadrant abdominal pain. Physical examination disclosed an elderly acutely ill woman. Her temperature was 100°F.; pulse, 112; and blood pressure 184/94. There was marked tenderness, spasm, and rebound tenderness in the right lower quadrant. The blood study revealed a hemoglobin of 60% and a white count of 10,000 with a shift to the left. Laparotomy was performed, and at operation the right ovary was noted to be replaced by a mass of tissue 6 cm. in diameter, deep purple in color with many loculated cysts containing hemorrhagic fluid. In one area, the tissue appeared more solid and pink. The uterus, left tube and ovary appeared normal. Right salpingoophorectomy and appendectomy were performed. Patient made an uneventful recovery and went home on the 16th postoperative day. The pathological studies were reported as hemorrhagic, infarcted granulosa cell tumor and subacute periappendicitis. Seventeen months later, this patient was readmitted because of acute intestinal obstruction. At operation, an adhesive band occluding the terminal ileum, was noted. The bowel at this point was gangrenous. Because of this and the additional incidental finding of a previously unsuspected adenocarcinoma of the cecum, an ileocolic resection was performed. No evidence of recurrent granulosa cell tumor was found. The patient expired on the 2nd postoperative day. Consent for autopsy was not obtained.

Case #2: R. S. I. #531164, a 46 year old white married nullipara was admitted because of the increasing size of her abdomen, the onset of which was noted three months prior to admission. Two years prior to admission, her menses had become highly irregular. A diagnosis of hyperthyroidism was established and subtotal thyroidectomy was performed ten months prior to the present illness. From the time of this operation until the present admission, menstruation was described as regular and normal. Physical examination revealed the abdomen to be enlarged to the size of an eight months gestation. Laparotomy was performed and at operation, the right ovary was found to be replaced by a septate cystic structure, 10 cm. in diameter, which had a smooth shiny transparent wall in places, but was mostly filled with cellular necrotic orange tumor tissue. The uterus and tubes were not remarkable; the left ovary was atrophic. Subtotal hysterectomy and bilateral salpingophorectomy were performed. The cystic mass was accidentally ruptured and the contents spilled in the peritoneal cavity. Pathological report was granulosa cell tumor with cystic degeneration and hyperplastic endometrium. At the time of the writing of this paper, the patient is alive and well, seven years postoperatively.

Case #3: S. G. #477259, a sixty year old white woman, para V, grava VI, ten years post menopausal, entered the hospital because of vaginal spotting, intermittent lower abdominal cramps and backache, of two months duration. She had, in addition, lost twenty-two pounds in the year prior to admission. Physical examination other than pelvic was not remarkable. Pelvic examination disclosed hypertrophic labia minora, a small normal anteverted uterus with a polyp extruding from the os, and in the region of the right adnexa, a hard movable cystic mass 5 cm. in diameter. Laparotomy was performed and the right ovary was found to be replaced by a purple, soft, cystic mass which presented yellow areas on section. The uterus was small and the left ovary atrophic. Right salpingophorectomy and excision of the polyp were performed. Pathological examination was reported as granulosa cell tumor of ovary and fibroadenomatous polyp of cervix. The patient is alive and well at the time of the writing of this paper eleven years postoperatively.

Case #4: G. S. #522199, a 48 year old white woman, para II, grava IV, was admitted because of increasing size of her abdomen. For the three years prior to her admission, her periods had become less frequent, occurring once every two or three months instead of her previously regular twenty eight day cycle. Physical examination revealed a distended abdomen with a fluid wave and "masses" that could be felt floating in the fluid. The vulva and vagina were cyanotic and on pelvic examination, the "masses" were noted to fill the cul-de-sac and the uterus could not be delineated. At operation, the abdomen was found to contain two gallons of serous fluid and "masses" of grayish cellular tissue arising from both ovaries. Biopsy report was sarcomatous granulosa cell tumor. The patient received a course of deep X-ray therapy but went rapidly downhill and expired ten weeks post-operatively. Permission for autopsy was not granted.

Case #5: M. K. #420280, a 57 year old white nullipara, with a history of hysterectomy five years prior to the present illness because of fibroids, was admitted because of lower abdominal pain, frequency of urination and dysuria. Physical examination revealed a large cystic mass, approximately 20 cm. in diameter, occupying the left side of the pelvis. Laparotomy was performed and a large bluish-brown cystic loculated mass measuring 12 cm. in diameter was noted in the midline in the pelvis, adherent to the sigmoid and to the pelvic wall. Another grayish granular yellow mass measuring 12 by 7 by 5 cm. was to the right of the first mass and also adherent to the pelvic wall. Most of the locules were filled with bloody fluid. Interspersed were areas of grayish yellow soft tumor tissue. In addition, there were other small hemorrhagic yellow nodules attached to the wall of the pelvis, the cecum and omentum. The uterus and left ovary were absent. Both large masses and all evident metastatic nodules were removed. Pathological examination revealed granulosa cell tumor with metastases. The patient expired one and a half years postoperatively with recurrent abdominal masses and ascites.

Case #6: M. J. #516016, a 53 year old white woman, para 1, grava 1, was admitted six years postmenopausal because of severe abdominal pain, mostly in the right lower quadrant, and radiating to the back and right shoulder, intermittent in nature for the nine

months prior to admission. Examination was completely negative except for a mass 5 cm. in diameter in the region of the right adnexa. At operation, the uterus and left adnexa were grossly normal. The right ovary was replaced by a bluish gray cyst bound down in the cul-de-sac by adhesions. Subtotal hysterectomy and bilateral salpingoophorectomy, and appendectomy were performed. The pathological report was granulosa cell tumor, trabecular type, hyperplastic endometrium, endometrial polyps, adenomyosis uteri, atrophic left ovary, chronic appendicitis. This patient was seen two months postoperatively and at that time was in good health. However, it has been impossible to locate her since then.

Case #7: A. S. M. #362321, a 50 year old white married nullipara, with a history of irregular menses throughout her life, was admitted seven years postmenopausal because she "felt lumps floating around" in her abdomen. Physical examination revealed an obese female with marked facial hirsutism. Examination of the abdomen revealed definite ascites and freely movable hard masses. Pelvic examination revealed an atrophic vulva and vagina and an irregularly enlarged uterus surrounded by the previously mentioned masses. At operation, large masses, 9 cm. in diameter, were found replacing each ovary. The uterus was slightly enlarged due to multiple fibromyomata. There was no evidence of metastases. Bilateral salpingoophorectomy and supracervical hysterectomy were performed. The pathological diagnosis was granulosa cell tumor of left ovary, fibromyoma of right ovary, fibromyomata uteri, atrophic endometrium. This patient is alive and well eight and one half years postoperatively.

Case #8: M. S. #596849, a 44 year old white woman, para III, grava II, (one set of twins), was admitted to the hospital with an eighteen hour history of severe abdominal pain, generalized, referred to the shoulders, and syncope. She had been amenorrheic for one year after an otherwise normal regular menstrual history up to that time. The blood pressure on admission was 100/0; pulse, 90; temperature, 99°F. Abdominal examination revealed generalized tenderness, spasm, and rebound tenderness. On pelvic examination, an exquisitely tender mass was noted in the region of the left adnexa. White blood count was 10,100 with a normal differential. At laparotomy, a large amount of clotted blood was found in the pelvis. The left ovary was the site of a yellowish brown well encapsulated tumor measuring 20 cm. in diameter. On its posterior surface there was a rent approximately 2 cm. in length. The right ovary appeared atrophic. The tubes were normal. Subtotal hysterectomy and left salpingoophorectomy were performed. Pathological report was "granulosa cell tumor of ovary, benign; atrophic uterus with small fibromyoma and Nabothian cysts". This patient is alive and well three years postoperatively.

Case #9: A. G. #288996, a white woman, para IV, grava IV, regularly menstruating was first admitted to the Mount Sinai Hospital January 21, 1924 when she was 43 years old. At that time, she had a history of abdominal pain, constipation, and fever of one week's duration. Examination revealed a cystic mass in the lower abdomen measuring 5 cm. in diameter. Laparotomy was performed and a left salpingoophorectomy for ovarian tumor was carried out. During the operation a loop of small bowel had to be dissected away from the tumor mass and was inadvertently opened and repaired. Pathological report at that time was "angiosarcoma of the ovary". She was again admitted in March 1928 because of a three day history of acute intestinal obstruction. Laparotomy was again performed and the obstruction found to be due to "adhesions and recurrence of tumor". The recurrent tumor was excised and another inadvertent perforation of the small bowel repaired. Pathological report was that of an "angiosarcoma". Menopause occurred after this operation. She was seen in the Follow-up Clinic and in January 1936 a mass was discovered in the right adnexal region. This increased in size and she was consequently given a course of deep X-ray therapy from July to September 1936. She was again admitted to the hospital in February 1938 complaining of abdominal pain of three months duration. Examination revealed a large irregular mass, 10 cm. in diameter, occupying the entire right pelvis and firmly adherent to the uterus. She was again explored and a large pelvic mass, probably ovarian, was noted extending retroperitoneally. The mass could not be

entirely removed and during the course of its partial dissection, the intestine was injured, necessitating resection and anastomosis of the ileum and ascending colon. The pathological report at this time was "malignant granulosa cell tumor with cystic degeneration". The slides of the former specimens were reviewed and in the light of the present knowledge were also reclassified as granulosa cell tumor. The patient was given another course of deep X-ray therapy from March to May 1938. During all this time she had minimal complaints referable to the neoplasm, chiefly mild right lower quadrant discomfort. She had no bleeding since her menopause in 1928, and was admitted in September 1938 for hormone studies, suction curettage and vaginal biopsy. The suction biopsy revealed proliferative endometrium; the vaginal biopsy was indicative of good estrogen activity; tests for the blood estrogen were negative; the urine estrogen was low (60 I.U./24 hours); and the urinary gonadotropic excretion was negative. This patient expired in another hospital on April 25, 1939, fifteen years and three months following her first admission. Postmortem examination revealed numerous intestinal adhesions, recurrent granulosa cell tumor (a mass 7.8 cm. in diameter adjacent to the uterus), a liver which was tremendously enlarged and studded with metastases, and a pyelonephritic contracted right kidney.

DISCUSSION

In this group of nine cases, the youngest patient was 43; the oldest 71; the average age being 52. Five of the patients had borne one or more children while four were childless. While all the factors to be considered in a sterility problem could not be determined from perusal of these records, this high percentage of barren marriages is in accord with the reported literature.

Although, as previously mentioned, these tumors may occur at any age, we are in agreement with Rhoades (17) that the great majority occur in the postmenopausal woman. Six of our nine cases were in postmenopausal women; one was in a woman in probable early menopause; and only two occurred in normally menstruating women, and even these were 43 and 46 years old respectively.

Abdominal pain was the predominant complaint, this symptom being recorded in the chief complaint of six of the nine patients. Indeed, two patients were admitted because of acute surgical abdomens, one of which was due to infarction of the tumor, and the other rupture of the neoplasm with hemoperitoneum. While acute abdominal symptoms may occur from torsion and infarction (11), hemoperitoneum is rare (29, 18).

The role of estrogens and estrogen producing neoplasms in the etiology of carcinoma has been investigated, discussed and reported by many authors, and the consequent not infrequent occurrence of granulosa cell tumors in association with hyperplasia and adenocarcinoma of the endometrium has been of great interest. Occasionally extragenital carcinomas are reported in association with this tumor and interestingly enough, in one of our cases an associated asymptomatic adenocarcinoma of the cecum was found. Of the four patients subjected to hysterectomy, in two cases the pathologist noted endometrial hyperplasia.

Much debate has risen concerning the degree of malignancy of granulosa cell tumors, and therefore the therapy to be recommended. In our series, the longest survival to date is eleven years with no sign of recurrence while another patient succumbed fifteen years after initial diagnosis. In view of the known fact that

patients may survive as long as twenty years or more before fatal recurrence, the prognosis in any individual case must of necessity be guarded. From the two cases who received radiotherapy, one can conclude that in the presence of widespread abdominal metastases, X-ray is of no benefit. On the other hand, the repeated X-ray therapy administered to our second case may very well have played a significant factor in prolonging her life fifteen years.

Three of our cases were treated by supracervical hysterectomy and bilateral salpingoophorectomy; one by supracervical hysterectomy and unilateral salpingoophorectomy; and four by unilateral salpingoophorectomy alone. Of these latter four, one patient had had a previous supracervical hysterectomy and unilateral salpingoophorectomy. In one obviously advanced case, only a biopsy was performed. It must be remembered that these cases date back as far as 1933, and this modicum of therapy no longer reflects our present attitude towards this neoplasm. It is our opinion that granulosa cell tumor of the ovary is a malignant neoplasm and should be treated, regardless of age, by total hysterectomy and bilateral salpingoophorectomy. The trend toward total, rather than subtotal hysterectomy, even in benign conditions, is now so widely accepted that it warrants no further discussion.

SUMMARY

In the years 1933-1949 inclusive, nine cases of granulosa cell tumor were operated upon at the Mount Sinai Hospital. These are reported in detail. The literature has been reviewed with regard to the histogenesis, etiology, pathology, incidence, and clinical picture of these tumors and conclusions drawn concerning their malignancy and recommended therapy.

BIBLIOGRAPHY

1. MEYER, R.: The Pathology of Some Special Ovarian Tumors and Their Relation to Sex Characters. *Am. J. Obst. & Gynec.*, 22: 697, 1931.
2. BUTTERWORTH, J. S.: *Am. J. Cancer*, 31: 85, 1937.
3. GEIST, S. H.: Histogenesis of Certain Ovarian Tumors and Their Biologic Effects. *Am. J. Obst. & Gynec.*, 30: 650, 1935.
4. DOCHERTY, M. B. AND MACCARTY, W. C.: Granulosa Cell Neoplasm with Discussion of Possible Histogenesis. *Am. J. Obst. & Gynec.*, 38: 698, 1939.
5. BISKIND, M. S. AND BISKIND, G. R.: *Proc. Soc. Exper. Biol. & Med.*, 55: 176, 1944.
6. LI, M. H. AND GARDNER, W. V.: Granulosa Cell Tumors in Intrapancratic Ovarian Grafts in Castrated Mice. *Science*, 106: 270, 1947.
7. PECKHAM, B. M., GREENE, R. R. AND JEFFRIES, M. E.: Granulosa Cell Tumors in Female Rats and Rabbits. *Science*, 107: 319, 1948.
8. NOVAK, E.: *Gynecological and Obstetrical Pathology*. Philadelphia and London, W. B. Saunders Company, 1947.
9. SPENCER, J. A. AND HOLLENBECK, Z. J. R.: Granulosa Cell Tumor with Presentation of 5 Cases, One with Associated Seven Months Pregnancy. *Am. J. Obst. & Gynec.*, 54: 281, 1947.
10. KLAFFEN, E.: *Arch. f. Gynäk.*, 150: 643, 1932.
11. HODGSON, J. E., DOCHERTY, M. B. AND MUSSEY, R. D.: Granulosa Cell Tumor; Clinical and Pathological Review of 62 Cases. *Surg., Gynec. & Obst.*, 81: 631, 1945.
12. DOCHERTY, M. B. AND MACCARTY, W. C.: Granulosa Cell Tumors with a Report of a 34 Pound Specimen and a Review. *Am. J. Obst. & Gynec.*, 37: 425, 1939.

13. JONES, G. E. S. AND TE LINDE, R. W.: Granulosa Cell Tumors; Curability. *Am. J. Obst. & Gynec.*, 50: 691, 1945.
14. VOGT, J. C.: Granulosa Cell Tumor of Ovary with Hemoperitoneum and Hemothorax, Report of Case. *Am. J. Obst. & Gynec.*, 40: 285, 1940.
15. DOCHERTY, M. B. AND MACCARTY, W. C.: Granulosa Cell Tumors with Observations on Radiosensitivity. *Am. J. Obst. & Gynec.*, 39: 147, 1940.
16. BIANCO, J. J. AND FAVORITE, G. O.: Granulosa Cell Tumor. *Am. J. Obst. & Gynec.*, 52: 677, 1946.
17. RHOADS, E. E.: Granulosa Cell Tumor; 5 Cases with Premature Menopause (Amenorrhea) and Recurrence of Menstruation. *Am. J. Obst. & Gynec.*, 51: 560, 1946.
18. BREWER, A. C.: Granulosa Cell Tumor as Acute Abdominal Emergency. *Brit. M. J.* 1: 49, 1948.
19. STABLER, F. AND THOMSON, J. G.: Granulosa Cell Tumor with Precocious Sexual Development in Child Aged 6. *J. Obst. & Gyn. Brit. Emp.*, 47: 199, 1940.
20. PARKS, J.: Granulosa Cell Tumors with Precocious Puberty. *Am. J. Obst. & Gynec.*, 36: 674, 1938.
21. AYRE, J. E. AND FOOTE, W. R.: Granulosa Cell Tumor with Pregnancy Following Removal. *Am. J. Obst. & Gynec.*, 51: 260, 1946.
22. COUNTISS, E. H.: Granulosa Cell Tumor Case Followed by Pregnancy. *Am. J. Obst. & Gynec.*, 36: 680, 1938.
23. SPEERT, H.: Granulosa Cell Tumor and Acromegaly. *J. Clin. Endocrinology*, 9: 630, 1949.
24. GEIST, S. H. AND SPIELMAN, F.: *J.A.M.A.*, 104: 2173, 1935.
25. PALMER, A.: Granulosa Cell Tumor, Estrogenic Hormone in Urine and Tumor. *Am. J. Obst. & Gynec.*, 37: 492, 1939.
26. INGRAHAM, C. B., BLOCK, W. C. AND RUTLEDGE, E. K.: Granulosa Cell Tumors; Relationship to Endometrial Carcinoma. *Am. J. Obst. & Gynec.*, 48: 760, 1944.
27. STOHR, G.: Granulosa Cell Tumor of Ovary and Coincident Carcinoma of Uterus (Role of Estrogen). *Am. J. Obst. & Gynec.*, 43: 586, 1942.
28. FINKLER, R. S.: Granulosa Cell Tumor with Carcinoma of Breast. *Am. J. Obst. & Gynec.*, 36: 1064, 1938.
29. WARD-McQUAIRD, J. N.: Hemoperitoneum Following Rupture of Granulosa Cell Tumor. *Brit. J. Surg.*, 37: 242, 1949.

BOOK REVIEW

The Scalp in Health and Disease. By HOWARD T. BEHRMAN, M.D. Quarto of 566 pages, illustrated, St. Louis, C. V. Mosby Co., 1952. Cloth, \$12.50

The importance of understanding the problems of the hair and scalp in health and disease called for a treatise of this kind. This well written and carefully organized book has already been recognized as an authoritative source of information in the field of normal and pathologic anatomy and physiology of the hair and scalp. The first chapter is devoted to embryology, anatomy and physiology. Aside from well known anatomic facts, it presents the most modern concepts of physiologic problems. Recent research and investigative studies relevant to the importance of sebum in the loss of hair as well as the effects of the steroids are discussed.

The second chapter deals with the care of the normal scalp. It presents detailed methods of shampooing and washing hair, the types and rationale for the various shampoos, hair lotions, hair creams, dyes and lotions. The techniques and mechanisms of wave lotions are thoroughly explained with descriptions of the precautionary tests which should be performed. Dermatitis following the application of sensitizing (allergenic) or irritating agents is discussed and its treatment regimen clarified. A chapter is devoted to the important subject of baldness. The author uses a classification which distinguishes between cicatricial and non-cicatricial alopecias. Numerous theories are advanced to explain ordinary male baldness. Genetic and hormonal factors are considered. The author believes that there exists a male-pattern alopecia which can be initiated by local diseases of the scalp and by systemic and glandular dysfunctions. A section concerning the medicolegal aspects of hair morphology has been added.

The seborrheic diathesis is divided into pityriasis simplex, steatoides and seborrhea oleosa. This is the most practical and simplest division from a clinical as well as etiological standpoint. The term seborrheic dermatitis is reserved for the acute, subacute and chronic inflammatory condition which develops upon a seborrheic soil. It is identical with the eczema seborrheicum of Unna.

In the chapter treating with infections of the scalp, every known type of infection due to pyogenic bacteria, spirochetes, viruses or fungi is mentioned. The discussion of scalp diseases due to fungi is especially thorough in pathology, etiology and treatment. The author follows modern concepts of the psychosomatic aspects of skin diseases in classifying some of the scalp disorders under: "Psychogenic Disorders of the Scalp"; he cautiously adds "Proved and Presumptive". These cases are well documented and the reader will become more conversant with the psychodynamics of skin diseases.

As many skin diseases include the scalp, the typical manifestations of these conditions are described. The final chapter discusses new growths of the scalp. They are classified similarly to cutaneous tumors elsewhere.

The book is supplemented by an appendix containing a wealth of well-tested formulas for shampoos, hair lotions, and scalp ointments. The text is easy to read and stimulating. The illustrations are well chosen and instructive. There is an extensive bibliography at the end of each chapter. This volume should be of great value to physicians concerned with the human hair in health and disease.

GEORGE KLEIN, M.D.

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CONTENTS

THE USE OF RADIOACTIVE GOLD IN THE TREATMENT OF EFFUSIONS DUE TO CANCER. <i>Norman Simon, M.D., Julian Abrams, M.D., Mansho Khilnani, M.D., Harold N. Margolin, M.D., Stuart I. Gurman, M.D., Joan Eliasoph, M.D., and Josephine Mayer, Ph.D.</i>	237
AN INTEGRATION OF THE PSYCHOSOMATIC VIEWPOINT IN MEDICINE. <i>M. Ralph Kaufman, M.D.</i>	247
ACCESSORY LUNG—UNUSUAL VARIATIONS. <i>Gabriel P. Seley, M.D.</i> ...	257
AFIBRINOGENEMIA IN PREGNANCY: DIAGNOSIS AND TREATMENT. <i>Herbert Chessin, M.D., and J. Conrad Greenwald, M.D.</i>	263
SOME GYNCOLOGICAL IMPLICATIONS OF THE CASTRATION COM- PLEX. <i>Bernard C. Meyer, M.D.</i>	267
FAILURE OF REPEATED INTRAPERITONEAL INJECTION OF HYALUR- ONIDASE TO PREVENT RECURRENCE OF ABDOMINAL ADHESIONS IN RATS. <i>Robert J. Wilder, M.D.</i>	278
THE MEDICAL TEACHING MISSION TO ISRAEL AND IRAN. <i>Leo M. Davidoff, M.D.</i>	280

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* Deceased

THE USE OF RADIOACTIVE GOLD IN THE TREATMENT OF EFFUSIONS DUE TO CANCER

NORMAN SIMON, M.D., JULIAN ABRAMS, M.D., MANSHO KHILNANI, M.D.,
HAROLD N. MARGOLIN, M.D., STUART I. GURMAN, M.D., JOAN ELIASOPH,
M.D., AND JOSEPHINE MAYER, Ph.D.

*From the Departments of Radiotherapy and Physics, The Mount Sinai Hospital,
New York City*

Radioactive gold has been used for several years to suppress the formation of pleural and peritoneal effusions due to malignant tumor. The results in the series of patients treated in the Mount Sinai Hospital correspond with the results obtained by others (1, 2, 3, 8). In addition to these confirmatory results some new observations on the distribution of radioactive gold are presented.

In 1950 Hahn and Goldie (4) showed that solutions of radioactive colloidal gold could prevent implantation of sarcoma in the peritoneal cavities of mice. Subsequent to this work numerous observers were able to demonstrate suppression of formation of serous effusions secondary to malignant tumors. A rather complete review of the available information on radioactive colloidal gold has recently been published (5).

Radioactive colloidal gold is used in serous effusions to selectively irradiate the lining membrane of the serosal cavity without effecting undue radiation to other portions of the body. Radioactive colloidal gold solution has been found suitable for this purpose because of the nature of its radioactive emissions and because of its behavior as a colloid. On disintegration Au^{198} emits a beta particle of 0.98 mev and gamma rays of 0.12 and 0.41 mev. The beta particles are absorbed in the first millimeter of serosal lining and deliver most of the biologically effective radiation. The gamma rays contribute a nonsignificant fraction of the radiation dose to the serous membranes, but their high penetration is advantageous, since they can be counted externally when the radioactive preparation is within the patient's body. A distinct disadvantage of the presence of penetrating gamma rays, however, is the hazard to personnel handling the isotope.

The radioactive gold used at the Mount Sinai Hospital is supplied by Abbott Laboratories and arrives as a colloidal solution in a bacterin bottle protected in a lead well. The activity of the purple-colored radioactive colloidal suspension is usually about 30 millicuries per cc. Transferring this solution to the patient presented a problem. The methods generally used provided protection from gamma rays by remote control apparatus or cumbersome lead shielded syringes. Needless to say, direct contamination by contact with the solution must be avoided. After preliminary experimentation with a number of transfer devices a simple method as indicated in figure 1 was adopted.

In assembling the apparatus in figure 1 the protective covering on the bacterin bottle containing gold is removed with long forceps, and alcohol is applied to the underlying rubber cap with a sponge on a long holder. A 16 gauge needle is then

pushed through the rubber cap into the air space above the level of the radioactive colloidal gold solution. Expendable plastic tubing connects this needle to a bottle of saline solution which is elevated about one meter above the gold. The three-way valve and 50 cc. syringe connected to the plastic tubing enables the operator to apply manual pressure if necessary.

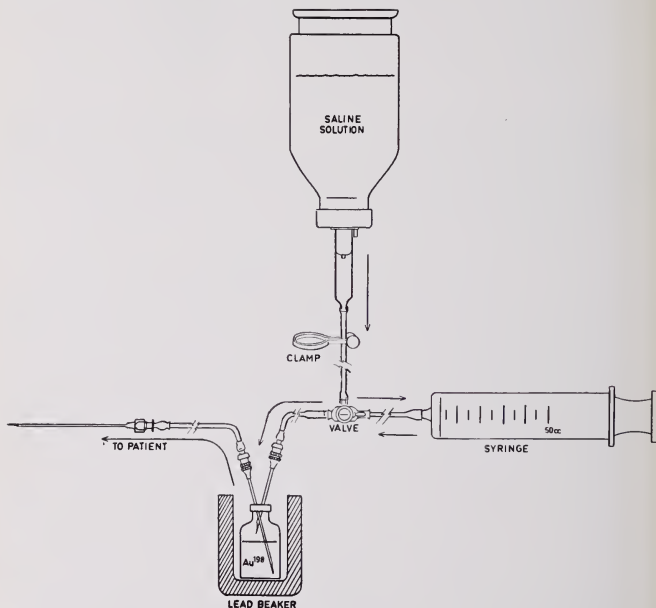


FIG. 1. Diagram of system used for displacing gold solution from bacterin bottle into patient. The plastic tube connections are expendable and standard supplies (Abbott Laboratories). The 50 cc. syringe in the system enables the operator to apply manual pressure if the gravity pressure from the elevated bottle is insufficient to displace the gold solution from the bacterin bottle fairly rapidly. The "hot" side of the system requires no handling while the gold solution is being displaced from the bacterin bottle in the lead beaker.

A longer 16 gauge needle attached to plastic tubing is pushed through the rubber cap to the bottom of the bacterin bottle. The plastic tubing connecting this needle is clamped tightly when the needle is inserted into the gold solution in order to prevent leakage. This tubing is then connected to a needle which has previously been inserted in the pleural or abdominal cavity. When the plastic tubes on both sides of the bottle of gold are unclamped the gold solution is displaced from its bottle into the patient by the saline solution from the elevated

reservoir. If the tubing connecting the gold solution and the patient fails to clear itself of the deep purple gold solution in about two minutes the 50 cc. syringe may be filled with saline, the valve turned appropriately, and the gold displaced more rapidly from the bacterin bottle by manual pressure on the syringe. When 100 cc. of saline solution is used to displace the gold the residual radioactivity in the bacterin bottle is insignificant.

This method has the virtue of expedience rather than originality, since other clinics have adopted it independently (1, 2). In this simple displacement of the contents of the bacterin bottle by water an individual dose must be obtained on each order of gold, for this method utilizes the entire contents of the bacterin bottle in the treatment of a single patient. This represents a disadvantage, but it is counterbalanced by the fact that handlers of radioactive gold in this hospital have received little radiation, no more than 5 milliroentgens to any part of the body (including hands), since the simplified technique was instituted.

TABLE I
Pleural effusions treated with Au¹⁹⁸

DIAGNOSIS	NO. OF PATIENTS	FAVORABLE RESULTS	NO EFFECT	UNCERTAIN
Carcinoma of breast	6	4	2	0
Carcinoma of lung	4	0	2	2
Lymphoma	3	2	1	0
Carcinoma of uterus	1	1	0	0
Total	14	7	5	2

RESULTS

Since July 1, 1951, fourteen patients with pleural effusions secondary to malignant tumor have received intrapleural injections of radioactive gold. The administered dose has ranged from 25 to 89 millicuries. The radioactive gold was injected following aspiration of most of the pleural fluid. All patients tolerated the injected gold well. In no instance did vomiting occur, and nausea was transient in only four patients. Peripheral blood cell counts were done at frequent intervals in some of the patients and no leukopenia or thrombocytopenia resulted.

Of the fourteen patients with pleural effusion, six had carcinoma of the breast, four carcinoma of the lung, three lymphoblastoma and one carcinoma of the fundus of the uterus. As can be seen from Table I, seven of these fourteen patients derived benefit from the radioactive colloidal gold treatment. Favorable results were manifested by a decrease in the frequency of chest taps to relieve dyspnea. A few of the favorable cases are worthy of more complete discussion in order to evaluate the efficacy of radioactive gold treatment.

E. M., a 70 year old white woman had had a left radical mastectomy in February 1950 for carcinoma of the breast with involvement of axillary lymph nodes. In July 1951, 16 months after operation, a left pleural effusion developed, and the resultant dyspnea re-

quired frequent chest taps for relief. From July 1951 to June 5, 1952, 32 thoracenteses were made, each time approximately 1,000 cc. of fluid were removed. Cell block examination showed carcinoma cells in this fluid. The patient gradually lost weight during the lengthy period when she was receiving the required chest taps, and pain developed in the anterior chest wall. On June 5, 1952, 1100 cc. of yellow slightly turbid fluid were aspirated from the left pleural cavity, and 45 millicuries of radioactive colloidal gold were injected into the left pleural cavity. Within a few weeks the rate of fluid formation in the pleural cavity was suppressed, and the patient enjoyed almost a full year of freedom from taps. On June 5, 1953, one year after the treatment with Au^{198} , dyspnea returned, and the chest was tapped again (Fig. 2).

M. V., a 44 year old Venezuelan housewife had a right radical mastectomy for adenocarcinoma with extensive axillary lymph node involvement in November 1951. In December 1951, approximately one month after operation, the patient developed a right hemiplegia which was considered due to cerebral metastasis. X-ray therapy was directed to the left cerebrum, and subjective and objective neurological improvement followed. In March 1952, four months after operation, a recurrence of carcinoma appeared in the skin of the

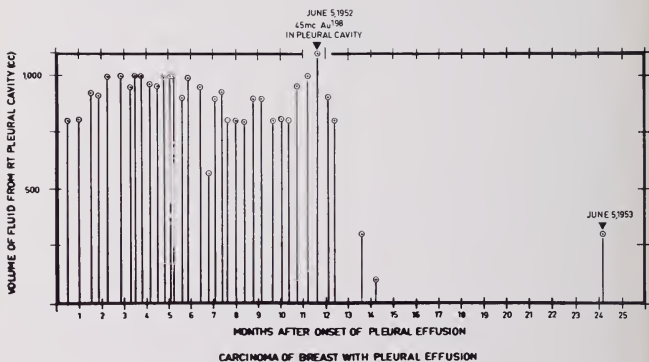


FIG. 2

chest wall adjacent to the mastectomy scar. This lesion was also treated with x-ray therapy. In August 1952 more nodules appeared in the chest wall, and a right pleural effusion developed. On August 7, 1952, a tap yielded 1,000 cc. of amber fluid which contained carcinoma cells. A tap was repeated two weeks later again yielding 1,000 cc., and 60 millicuries of radioactive gold were injected into the right pleural cavity. The patient left the hospital and remained free from dyspnea for seven months after the injection of radioactive gold. In March 1953 fluid re-accumulated and necropsy showed widespread metastases involving the liver, right pleura and mediastinum. Fibrous adhesions were present in the right lower chest between the visceral and parietal pleura, while the untreated left side was free from adhesions.

C. N., a 68 year old single female was admitted to the Mount Sinai Hospital in January 1953 for dyspnea due to a left pleural effusion. The left breast was the site of a large inflammatory carcinoma, and the left axillary lymph nodes were enlarged. For relief of dyspnea left chest taps were made on January 20, 25, and February 10, yielding approximately 1,000 cc. of clear yellow fluid at each tap. On February 20, 1953, 1100 cc. of bloody

fluid were removed from the left chest and 89 millicuries of radioactive gold were injected into this pleural cavity. Continued chest taps were required for relief of dyspnea for the next eight weeks. At each tap except the last, approximately 1,000 cc. of fluid were removed. The last tap on April 10 resulted in a yield of only 600 cc. of fluid, and since that time there has been no significant re-accumulation of fluid in the left pleural cavity. The right pleural cavity, however, which had previously been clear, now developed massive effusions requiring frequent tapping of 1500 to 2000 cc. every 7 to 10 days. On April 15, 1953, 10 mg. of nitrogen mustard (0.2 mg. per kilogram of body weight) were injected into the right pleural cavity after removal of 1500 cc. of fluid. Two hours after this injection the patient had severe nausea and vomiting lasting three hours. Following the nitrogen mustard

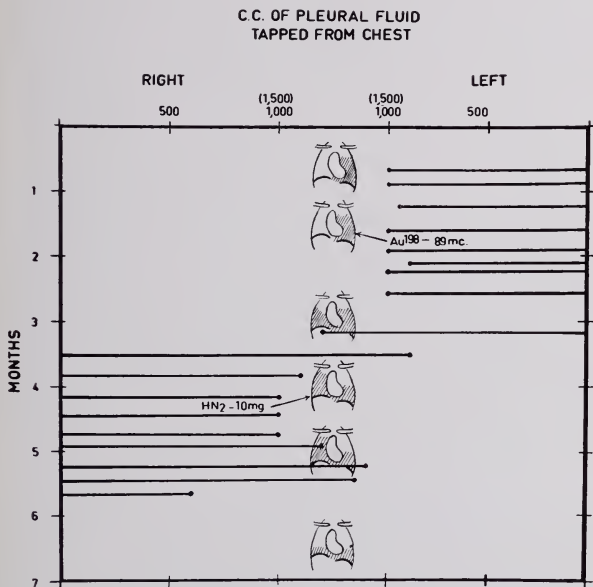


FIG. 3

treatment taps were required for eight weeks at the end of which time further taps were not indicated. In this patient the suppression of the accumulation of fluid was similar in both pleural cavities, one receiving Au¹⁹⁸ and the other nitrogen mustard (Fig. 3). At necropsy pleural adhesions were more extensive on the gold-treated side.

Along with those patients who have responded favorably to the radioactive gold treatment there have been others in whom this treatment has made no discernible change. Although definite conclusions cannot be drawn from this

small series of treatments, this experience confirms that of others that better results are obtained in carcinoma of the breast with effusion than in carcinoma of the lung with effusion (2).

Attempts were made to treat the pleural effusions of three other patients not listed in this series, but gold was not injected because of loculation of fluid. It was felt hazardous to inject large quantities of radiation into loculations in the pleural cavity which might have contained the radioactive colloid in great concentration.

Ascites has been treated in five patients with abdominal carcinomatosis, and three of these patients have shown beneficial effects. Data from these cases have been used in studying the distribution of gold in the body.

The distribution of gold in the pleural or peritoneal cavity can be estimated qualitatively and even quantitatively by making external counts with a G/M

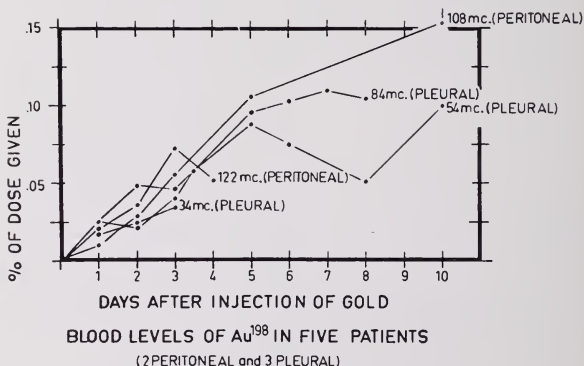


FIG. 4

tube (1). An indication that the activity is diffuse, rather than loculated in a cavity, can also be obtained by whole body radioautography. In this method a photographic film is exposed by the gamma activity of the radioactive gold when the patient is placed on the film for a suitable length of time (about 100 milli-curie minutes). Before removing the film a conventional x-ray exposure is made to identify the body regions of greatest gamma activity.

The dose of radioactive gold has been established empirically in a considerable number of clinical applications. It is of interest to attempt an estimate of dose in roentgens for comparison with other radiation techniques. Chamberlain (5) has estimated a beta dose of 3,000 roentgens equivalent physical to the surface of the peritoneum when 100 mc. of radioactive colloidal gold are injected. This dose in roentgens assumes the surface of the peritoneum to be 30,000 square centimeters. Walton and Sinclair (1) of England have investigated dosimetry including the

effect of various volumes of peritoneal fluid. These observers are in agreement with Chamberlain when the volume of fluid in the abdomen is approximately 1,000 cc.

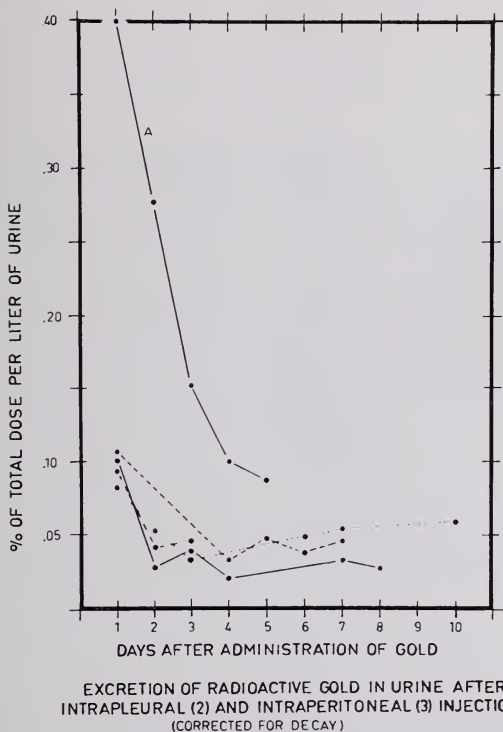


FIG. 5. Curve A pertains to a patient whose total urinary output was low (120 to 300 cc. daily). The absolute excretion of Au^{198} in this instance is approximately equal to the amount observed in the remaining patients who excreted normal quantities of urine.

Other workers (6) note that little of the radioactive gold colloid escapes from its contained serosal cavity into the blood, urine, or feces. Specimens of venous blood were drawn from five patients receiving radioactive gold in a serosal cavity, and figure 4 indicates that less than 0.2 per cent of the given doses was detected in the circulating blood at any time within the first ten days. These

determinations were made by measuring the activity in a 4 cc. sample of whole blood and assuming the total circulating blood volume to be 5 liters. The decay is corrected to refer to the date of administration of the radioactive gold.

When cells are separated from the plasma in the blood all the gold activity is in the plasma. Precipitation of the plasma with trichloroacetic acid indicates that the radio-gold is protein-bound. The white cells circulating in the blood do not contain measurable amounts of gold.

The urinary excretion of intrapleural or intraperitoneal gold colloid is considerably higher on the first day than on subsequent days. From the data in figure 5,

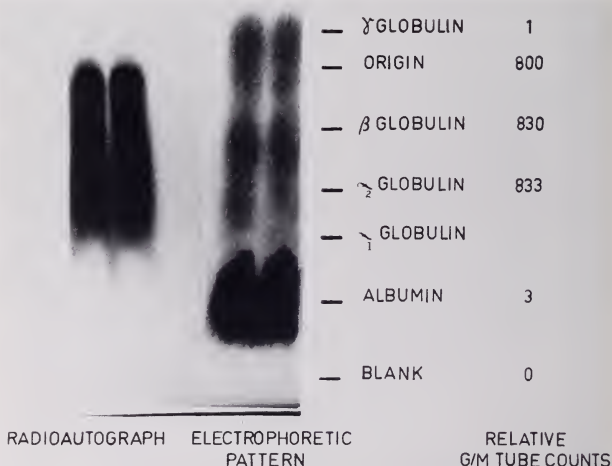


FIG. 6. Radioactive colloidal gold added in vitro to normal plasma (500 mc Au^{198} to 200 cc. plasma). Proteins were separated by filter paper electrophoresis and radioactivity in separated protein fractions was counted with G/M tube (window 5 mgm/cm^2). Distribution of radioactive gold restricted to α and β globulin is indicated in the radioautograph. Activity is also present at the point of application (origin) of the droplet of plasma.

pertaining to five patients whose excretion was studied sufficiently for inclusion in these data, 0.1 per cent of the administered gold is excreted in the urine the first day. The high early excretion of gold in the urine is difficult to explain, but may be attributable to the immediate excretion of free gold, while the protein-bound gold is excreted in the urine in accordance with its level in the blood.

To locate the radioactive gold in the blood plasma the technique of filter paper electrophoresis was used (7). Samples of blood serum, plasma, peritoneal and pleural fluid containing Au^{198} were applied to filter paper, and the proteins were separated (7). Radioautography of the electrophoretic pattern and direct

counting with a thin-window Geiger-Muller tube show the gold in α and β globulin fractions; the γ globulin, albumin and fibrinogen do not contain gold. Appreciable amounts of radioactive gold remain at the origin of the sample droplet, uninfluenced by the migration of proteins in the electrophoretic process. Radioactive colloidal gold in solution as shipped from Abbott Laboratories fails to migrate during electrophoresis.

When colloidal gold solution is added to blood plasma *in vitro*, the gold is bound to protein fractions in plasma (see fig. 6). This distribution also applies to ascitic and pleural fluid.

DISCUSSION

Intrapleurally injected radioactive gold prevents re-accumulation of fluid in a significant proportion of patients treated. Similar indications of benefit in 25 to 50 per cent of patients treated have been reported. As a beta particle emitter for the irradiation of serosal surfaces, however, radioactive colloidal gold has two disadvantages. The first disadvantage is due to its gamma ray activity. In radiating a serosal surface with beta particles little is to be gained by the addition of a gamma ray which serves chiefly to limit the facility and ease with which the isotope may be handled. The second disadvantage to Au^{198} is its short half life of 2.7 days. Such rapid decay requires too carefully scheduled manufacture, delivery, and use.

It is possible that the effect of radioactive gold in suppressing pleural effusions can be duplicated by non-radioactive substances. Some investigators have been evaluating the effect of intrapleural nitrogen mustard for this purpose. Our experience, limited to four cases, indicates that, when nitrogen mustard is injected intrapleurally in doses of 0.2 to 0.4 mg. per kilogram of body weight, transient vomiting and weakness follows. Such severe reactions have not been seen in patients treated with intrapleural radioactive gold. Our single opportunity to treat a patient with bilateral effusions by both methods (see patient C. N. above) showed no appreciable difference clinically in the effects obtained from the use of gold and mustard.

Despite the usual difficulty of evaluation of palliative results in the treatment of cancer, benefits derived from radioactive gold in effusions are apparent. Respite from paracenteses is a clear cut indication of benefit. Statistics concerning percentage palliated are here not so important as clinical appraisal of individual cases. In this way one develops the impression that gold is best suited to the patient whose cancer is slowly growing and in whom the accumulation of fluid is the most important symptomatic manifestation of disease. Pleural effusion in slowly growing carcinoma of the breast and ascites in ovarian carcinoma represent good indications for the use of radioactive gold. It has also been suggested that this treatment may be helpful at operation when the contents of a cystic carcinoma of the ovary are spilled in the peritoneal cavity. In this instance radioactive gold may prevent implantation and growth of the spilled malignant cells.

CONCLUSIONS

1. The accumulation of pleural and peritoneal effusions secondary to malignant tumor is appreciably suppressed in half of the patients treated by radioactive colloidal gold solution injected into the pleural or peritoneal cavities.

2. No important side reactions have been observed in the 19 patients discussed in this paper.

3. The radioactive gold in the circulating blood is less than 0.2 per cent of the injected dose in the peritoneum or pleura.

4. The gold in the blood is protein-bound to the α and β globulins as demonstrated by filter paper electrophoresis.

The authors gratefully acknowledge the assistance of Dr. Sam Levin and Dr. Lena Sharney.

BIBLIOGRAPHY

1. WALTON, R. J., AND SINCLAIR, W. K.: Intracavitary Irradiation with Radioactive Colloidal Gold in the Palliative Treatment of Malignant Pleural and Peritoneal Effusions. *Brit. Med. Bull.*, 8: 165, 1952.
2. KING, E. R., SPICER, D. W., DOWDA, F. W., BENDER, M. A., AND NOEL, W. E.: The Use of Radioactive Colloidal Gold (Au^{198}) in Pleural Effusions and Ascites Associated with Malignancy. *Am. Jour. of Roent., Rad. Ther. and Nuc. Med.*, 68: 413, 1952.
3. ROSE, R. G., OSBORNE, M. P., AND STEVENS, W. B.: The Intracavitary Administration of Radioactive Colloidal Gold. *New Eng. Jour. Med.*, 247: 663, 1952.
4. GOLDIE, H., AND HAHN, P. F.: Distribution and Effect of Colloidal Radioactive Gold in Peritoneal Fluid Containing Free Sarcoma 37 Cells. *Proc. Soc. Exper. Biol. and Med.*, 74: 638, 1950.
5. TABERN, D. L., GLEASON, G. I., AND SAVOIE, M. J.: A Manual on the Properties and Experimental Use of Radioactive Colloidal Gold-198. Abbott Laboratories, 1951.
6. ANDREWS, G. A., ROOT, S. W., AND KINSLEY, R. M.: Metabolism and Distribution of Colloidal Au-198 Injected into Serous Cavities for Treatment of Effusions Associated with Malignant Neoplasms. *Cancer*, 6: 294, 1953.
7. GORDON, A. H., GROSS, J., O'CONNOR, D., AND PITT-RIVERS, R.: Nature of the Circulating Thyroid Hormone-Plasma Protein Complex. *Nature*, 169: 19, 1952.
8. ANDREWS, G. A., ROOT, S. W., KERMAN, H. D., AND BIGELOW, R. R.: Intracavitary Colloidal Radiogold in the Treatment of Effusions Caused by Malignant Neoplasms. *Ann. Surg.*, 137: 375, 1953.

ERRATUM

In the article by Rosenfield, R. E. and Vogel, P. entitled "Newer Knowledge of Human Blood Factors", *J. Mt. Sinai Hosp.*, 22: 89, (July-Aug.) 1953, a line was omitted. On page 95 between lines 18 and 19 the following should be inserted: . . .allow for saliva typing (45). When an A-B-O secretor is devoid of Lewis substance. . . .

AN INTEGRATION OF THE PSYCHOSOMATIC VIEWPOINT IN MEDICINE*

M. RALPH KAUFMAN, M.D.†

Mr. Chairman, Ladies and Gentlemen:

It gives me great pleasure and satisfaction to appear before you at this the last lecture in the series on "The Recent Advances in Psychosomatic Medicine". It was particularly appropriate that this series should be under the aegis of Dr. Eli Moschowitz who, as you know, has been one of the early pioneers in this field. Most of you are undoubtedly familiar with his publications and certainly with his point of view.

A discussion of the integration of the psychosomatic point of view in medicine would certainly involve the primary question of what is psychosomatic medicine. The mere titles of the papers already presented in this series are an indication of the breadth of the field. We have heard a discussion of what appear to be clinical entities like obesity (1), hyperthyroidism (6), diabetes mellitus (3), and hypertension (16). There has been a paper on psychophysiological studies of fistulae in the gastrointestinal tract (7) and a paper on experimental psychiatry (10). In addition we have had a discussion on the essentials of psychotherapy (5), so that we have ranged through the clinical, to the research and the therapeutic aspects of the problem.

Perhaps some light may be thrown on our present-day status if we make some attempt, no matter how cursory, to trace our genealogy. The most recent impetus in the field of so-called psychosomatic medicine has come primarily from the psychiatrist and only secondarily from the internist. However, it has been the internist or his reasonable facsimile, the general practitioner, who, dealing with somatic illness, has always recognized, in one way or another, that there is an interrelationship between soma and psyche. He has phrased this in many ways, either as directly etiological or as a series of parallel, coincidental events that on occasion have impinged on each other, or at times his point of view has been a holistic one. Nevertheless, there has always been this awareness.

It is customary in discussions of this sort to bring in whatever historical knowledge the speaker happens to have and to point out that traditionally physicians have descended from the witch doctor, the shaman or priest. I, myself, have done this on many occasions. The implication, of course, is that since our ancestors treated by incantation and exorcisement the psychic factor in the disease process has always been recognized. Indeed, it would seem on superficial examination as if at one time in the history of medicine psychogenic factors were the only ones that were considered. I now believe that to a certain

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† Psychiatrist to The Mount Sinai Hospital, New York City and Clinical Professor of Psychiatry, College of Physicians and Surgeons, Columbia University, New York City.

extent this is a misreading of medical history. Since I am not in any way an expert in this field, I shall have to give you what is after all merely a superficial impression. I wonder, however, as to whether the priest who treated by incantation felt that he was dealing only with psychological and emotional factors or whether to him possession by a demon did not presuppose an actual physical entity. An angry god or a vicious demon may very well have symbolized a series of strictly physical factors which have nothing to do with psychogenesis in the sense that this has been utilized in modern times.

Sigerist (15) in his most recent book on the history of medicine has asked the question, "How can a man make another individual sick?" and pointed out that two of the oldest and most basic concepts of disease indicated that a disease is a "plus or minus", a "too much or not enough"; that a man is sick because there is something in his body that did not belong there or because something was removed from him that was necessary to life. A foreign object could be introduced by magic into a victim's body, or a vital part could be removed by magic. Object intrusion as a primary cause of illness is very widespread. Such objects might be shot into the body and could be of varied nature—"a small pebble, a bit of straw, leather, earth, coal, a shell, an insect, a worm or other small animals". The therapy in such an instance would consist of counter-magic practiced by a specialist in the field. In many instances, however, it was felt that it was not the object itself that caused the illness but the magic inherent in the object. We thus have a spectrum of etiological factors in which physiological and psychological factors may be intermingled in any given case.

There is, however, the other side of the coin which goes back to the concept of a duality of the person, namely, the soma and the soul. Here one enters into an area in which psychological factors in the broadest definition seem to have been taken into consideration. Indeed, a good deal of the difficulties that confront us today seem to be related to this duality, and one questions as to whether modern medicine has ever really broken the chains of theologico-, philosophico-somatic interrelationship. Some of the hostility of the late 19th century and early 20th century materialistic scientists toward the role of emotional factors grew out of this duality. Having dispensed with the soul there was a tendency to also dispense with the psyche because by analogy one was the same as the other.

In addition, as we all know, the change in basic concepts of pathology which is usually credited to Virchow began to play a role, and a sort of materialistic mechanization became the scientific method in biology and especially in medicine. The totality of the organism was broken down and one began to study disease rather than people. The macroscopic and microscopic pathological diagnosis became the end in all, and wherever the clinical symptoms and signs could be correlated with a pathological lesion, in most instances this was considered as the way to total knowledge of the disease.

Some time ago, Dr. Paul Klemperer told another audience in this auditorium that when he was confronted with a problem he came to see me in order to help him arrive at a decision. He apparently was quite pleased with my help, since I

recognized quite early in our discussion what he really wanted to do, and so I ended up by advising him to do exactly that. Amongst other things the result was a most delightful talk on problems in Israel. In relation to this particular discussion I went to Dr. Klemperer and spent some time discussing some of the modern ideas and changes in regard to illness. He indicated that there has been a very fundamental change in biological concepts especially those relating to health and disease; that one no longer looked for a single etiological factor as the only cause of disease; that in reality it was necessary to have a knowledge of the phylogenesis and ontogenesis of the individual in order to be able to understand what was happening to him at any given moment; and that certainly a knowledge of the total individual included his psyche in terms of his endowment and life experiences; that one must think in terms of multiple factors and that psychogenesis does not imply the single factor in a total reaction but is one of the factors in a total picture. It must be remembered that each one of these factors has its own history and in order to understand what takes place at any given moment in the individual one would have to know the total history of that individual. A sort of biological bridge of San Luis Rey.

This then brings us to an attempt at a definition of psychosomatic medicine, and for this I can do no better than to quote Margolin and myself (9) concerning such a definition. "Psychosomatic medicine is an operational approach to the theory and practice of medicine in which the structure and function of the psychic apparatus are dealt with as a variable in health and disease, just as, for example, are physiology and pathology. It is apparent that this definition requires that the psychological factor be homogenized into every aspect of the approach of a physician to a patient and into the pathogenetic conception of the disease process. It specifically denies the type of thinking in which the psychological factor is considered as a separate layer or as an afterthought in the evaluation of the patient. To further implement this psychosomatic formulation of the theory and practice of medicine, an illness can be divided into the following phases with respect to the psychological factor: 1. The pre-morbid personality in terms of the social, economic, somatic and psychosexual adaptation of the patient, including the presence or absence of frank neurotic or psychotic symptoms. 2. The onset of symptoms. 3. The latent period of the disease, i.e., the interval between the beginning of the disease process and the point at which the patient seeks help. 4. The reaction of the patient to the therapist and to therapy. 5. The reaction of the therapist to the patient. 6. The course of the disease. 7. The postmorbid state, i.e., convalescence and recovery or invalidism." This definition has certain important consequences since it does not necessitate the revision of our fundamental medical scientific thinking and eliminates a tendency to conceive of the psychological factor from an exclusively etiological point of view.

In the papers that have constituted this series we have had several that dealt with such metabolic disorders as obesity, diabetes mellitus, and hyperthyroidism. There was a paper dealing with neurohumeral mechanisms involving cardio-vascular disorders of which hypertension is an outstanding example. In

these presentations we were exposed to different points of view as expressed by different schools of thought. The crucial difference lay in the system of human psychology to which a given school subscribed. The Cornell group of Wolff and his associates bring to bear a point of view which is closest to that of the psychobiology of Adolf Meyer. There are points of view which emphasize the role of personality structure in the etiology of so-called psychosomatic disease. Others such as Alexander stress the specificity of conflict. Still others emphasize the conditioned reflex. Margolin, Grinker, Mirsky and others emphasize de-compensated psychophysiological moods and affective states. All of these viewpoints have validity and undoubtedly will prove to be different aspects of some basic correlating theoretical synthesis.

I am primarily interested today in presenting the positive aspects of our knowledge rather than the divergence of the points of view. However, in order to do this one must take cognizance of the limitations of our knowledge which in turn will bring us to the forefront of our actual knowledge. A basic theoretical frame of reference becomes essential at a given point in any scientific methodology. The psychoanalysis of Freud has given us such a frame of reference. Certain outstanding contributions that have come from psychoanalysis gave an orientation and an observational capacity to the workers in this field without which there is a limitation in the data which is reported. It is not a matter of academic importance only as to whether one works with a concept of an unconscious which is limited to a mere lack of awareness or with a concept of the unconscious which involves a totally different system of reference. The unconscious of psychoanalysis is a dynamic concept involving certain laws of mental functioning—the concept of the primary process, timelessness; a system of energy; and a relationship to other institutions of the mind. Utilizing this concept one is enabled to make certain observations and thus accumulate certain data which is impossible to accumulate in any other way. The knowledge of unconscious motivation enables us to demonstrate the genesis of psychophysiological processes. This has been demonstrated on many occasions in this field, especially by the work of Mirsky (11, 13), Grinker (13) and our own work and experimental study of individuals with gastrointestinal fistulae (4, 8). In the latter work, which has been reported to you in this series, it was only through a series of psychoanalytic observations that the relationship of the unconscious to physiological functioning could be observed and certain inferences and hypotheses set up as a result.

There is another contribution from psychoanalysis which is of course familiar to all of you which has had a profound influence in medicine, especially in relation to the art of its practice, and that is the knowledge of the transference and counter-transference phenomena. It would be redundant to reformulate these two concepts for this audience. I should like to draw attention only to the opportunity for the scientific humanization of medical practice which this knowledge affords us.

To turn to another area. As you know, there have been great advances recently in the field of neurophysiology. This is exemplified by a series of articles

reported in the February 1952 Archives of Neurology and Psychiatry. Neurological concepts have been changing gradually from a static neuro-anatomic localization basis to those involving dynamic, interacting functioning. Nevertheless, certain tendencies have arisen that make for a misconception. Knowledge, even if true and available, as to the functioning of the brain as a computing machine may lead one in the direction of surmising this as a final answer that would lead science into a blind alley. The telephone circuit analogy has again become popular, and to utilize this crude model for purposes of discussion one would have to state that all the knowledge concerning the wires, electrical circuits, exchange and automatic dialing would still not vitiate the fact that what is important is what is fed into the system. Who says what to whom and how many people are listening in on the party line? What they hear and what the relationships are to each other is the significant matter. A computing machine can only accomplish what it has been set up to do and can deal only with that which has been fed into it.

Lashley in his discussion of Penfield's paper (12) has put the matter succinctly. "I am less impressed with the analogies of various machines and neural activity, such as are discussed in 'cybernetics'. There has been a curious parallel in the histories of neurological theories and of paranoid delusional systems. In Mesmer's day the paranoic was persecuted by malicious animal magnetism, his successors, by galvanic shocks, by the telegraph, by radio, and by radar, keeping their delusional systems up-to-date with the latest fashions in physics. Descartes was impressed by the hydraulic figures in the royal gardens and developed a hydraulic theory of the action of the brain. We have since had telephone theories, electrical-field theories, and, now, theories based on the computing machines and automatic rudders. I suggest that we are more likely to find out how the brain works by studying the brain itself and the phenomena of behavior than by indulging in far-fetched physical analogies. The similarities in such comparisons are the product of an over-simplification of the problems of behavior.

"Dr. Penfield's observations on the effects of stimulating the temporal lobe raise many problems, but I do not believe that they justify the conclusion that memories are stored specifically in that region. He finds that removal of the excitable area does not destroy the memory which can be elicited from that area, and he explains this fact by assuming a bilateral localization. A bilateral temporal lobectomy in the monkey produces a badly deteriorated animal, who seems to have forgotten his previous training. But we find that training after operation on a new and different habit will restore his memory for similar habits, which he seemed to have lost. Thus, if the memory for differential reactions to a number of black and white visual forms or pictures seems to have been destroyed by lobotomy, and the monkey is trained after operation on the discrimination of red and green, this training produces spontaneous recovery of the other memories for uncolored forms. This is true for bilateral lesions of the temporal lobe; it is true also for bilateral lesions in any part of the posterior association areas. Such evidence seems conclusive that the memory traces are not stored exclusively in the temporal areas."

Thus, even when every aspect of the transmission of the impulses in the neuro-humeral system is known, the life experiences of the individual will be the most important factors in the total reaction of that individual. The recognition of this will obviate most of the artificial conflict between the organicist and functionalist. The hypothetical neural pattern in which identification is registered is of less importance and is of a secondary order to the fact of identification. (Parent with heart disease.) The approach which is phrased purely in terms of the number of brain cells and their patterning is somewhat like judging a book's meaning purely by analyzing the grammar, the syntax, and the counting of the letters of the alphabet that go to make up the sentences.

Penfield's remarkable observations on electrical stimulation of the temporal lobes which evokes memory patterns are a basic contribution. However, as yet they tell us little of the meaning of these experiences although as emphasized by Kubie they open an avenue for the combined research effort of the psychiatrist and neurophysiologist.

It is of interest in relation to my earlier comments concerning the question of soma and soul to quote the last two paragraphs of Penfield's stimulating article. "If anywhere, it is in the centrencephalic system that Hughlings Jackson's 'highest level' of functional integration is to be found. But the circuits of this system run out to the various functional areas of the cortex and back again. The memory cortex forms one of these areas. In a very real sense, there is no 'higher' and no 'lower' in this system. The 'place of understanding' is not walled up in a cell or in a center of gray matter. It is to be sought in the perfect functioning of all these converging circuits.

"The demonstration of the existence of cortical 'patterns' that preserve the detail of current experience, as though in a library of many volumes, is one of the first steps toward a physiology of the mind. The nature of the pattern, the mechanism of its formation, the mechanism of its subsequent utilization, and the integrative processes that form the substratum of consciousness—these will one day be translated into physiological formulas.

"But when that day dawns, I surmise that men will still stand in doubt before the ultimate riddle—What is the bridge between nerve impulse and thought? And what about a man's soul?"

Sherrington (14), in his Gifford Lectures, recently republished, which incidentally are presented with extraordinary charm and almost lyrical beauty, formulates the present status of this aspect of the problem as follows. "The student of the mind, for instance the practical psychiatrist at the mental hospital, must find the physiology of the brain still remote and vague for his desiderata on his subject. He may have hoped from it some knowledge which would serve to found the norm from which psychopathology could take its points of departure in this direction or that. There is for instance the condition 'anxiety'. None is I suppose more far-reaching as a warper of the mind. But where does neurophysiology contribute anything to the knowledge of the norm from which anxiety causes departure, and what has cerebral physiology to offer on the whole subject of 'anxiety'? The psychiatrist has perforce to go on his way seeking

things more germane to what he needs. The mind is a something with such manifold variety, such fleeting changes, such countless nuances, such wealth of combinations, such heights and depths of mood, such sweeps of passion, such vistas of imagination, that the bald submission of some electrical potentials recognizable in nerve-centres as correlative to all these may seem to the special student of mind almost derisory. It is, further, more than mere lack of corresponding complexity which frustrates the comparison."

It cannot be emphasized too strongly that the field of medicine is beset with extraordinary complexities. In the particular area which is under discussion tonight there has been a tendency to over-simplify, as a result of which false correlations have been set up which only give the appearance of truth and in some instances have resulted in rather disastrous illusion. A kind of spot-check method of research has developed. It must be emphasized that the psychological observations must of need be of the same order of validity as the physiological ones. There are many methodological difficulties and of course great deficiencies in our knowledge. Any advancement of science means a review of what we have known in terms of what we have just found out which may lead to an operational concept for the next step which is based on what we know plus a little speculation plus synthesis. In spite of the differences in schools of thought and basic approaches, certain fundamental observations are available. Regardless of what the ultimate explanations may be there is today a body of knowledge which cannot be controverted, which indicates that there cannot be any dichotomy between mind and body, that there is an intimate relationship between psyche and soma, that life experiences are significant for the individual in terms of his total psychobiological functioning, and that psychological phenomena are an integral part of the functioning whole and that they cannot be left out of consideration if one is to understand any aspect of an organism's function. This brought out in a rather striking way by Hinkle's paper on diabetes. His charts demonstrated the temporal relationship between subtle biochemical functions and emotional situations, that the blood sugar curve, the utilization of ketones and glucose are part of a total function and fluctuate with the emotional experiences of the individual. This has tremendous implications for teaching in medicine.

Psychiatry has now become one of the basic sciences in medicine and in many medical schools is being integrated into the curriculum as such. The psychiatrist's role is that of an integrator and catalyst, and he cannot be relegated in the teaching program to a 20 to 30 hour lecture demonstration series of deteriorating dementia-praecox patients. Some 15 years ago Felix Deutsch, Blumgart and I (2) conducted a study of the problems of teaching in this field which led to a formulated teaching program in which there was a collaboration between psychiatrists and internists. This was carried out at the Beth Israel Hospital in Boston over some years under the aegis of the Josiah Macy, Jr. Foundation. "Allowing for the natural variations in psychological aptitude of the individual student and in spite of—difficulties—, it was possible, through an intensive and persistent program of teaching based on the (psychoanalytic) concepts outlined,

to familiarize the student with the basic principles of psychosomatic medicine. The intimate interactions between psychological and somatic factors in the psychosomatic unit were grasped. He (student) was able to a gratifying degree to evaluate the various components which are essential in understanding both the patient and his disease; to evaluate the current conflict; to relate this latter in dynamic terms to the old conflicts and personality patterns; to give proper weight to the secondary gain involved in the illness; to see the personality in perspective in terms of its structure; to evaluate, on the basis of positive evidence, the psychoneurotic symptomatology; to elicit pertinent data without descending to aimless hit or miss questioning; to maintain an objective, neutral attitude toward the patient's emotional problems; to guard against the projection of the examiner's own conflict; to evaluate as a totality the individual who is ill rather than to emphasize the system which shows pathology; and to evaluate the therapeutic possibilities in terms of the needs and potentialities of the patient, rather than to rely upon the vague and imponderable 'personality of the doctor'." The basic concepts with which he deals have to become part of the student's knowledge not only in the clinical but as part of his fundamental teaching in physiology, bio-chemistry and other pre-clinical subjects. Indeed, in most instances the most complete appreciation of these subjects can only come if this point of view is integrated with the teacher's own knowledge.

I can remember an experience of my own in medical school when our team in pharmacology was given the task of determining the effect of amyl nitrite on blood pressure. As is well known to you, the physiological effect of amyl nitrite is to cause a very drastic fall in blood pressure. The subject of the experiment, a member of our team, was an individual who stuttered, was tense and fearful, especially under pressure. He was selected to inhale the nitrite. On the breaking of the pearl and on inhalation, instead of a fall in blood pressure there was a tremendous rise which was recorded on the Kymograph. At this point our instructor in pharmacology appeared, noted the result and bawled us out for having spoiled the experiment. It had to be repeated subsequently on our own time. I have never forgotten this since it was really a remarkable opportunity to demonstrate to the class the effect of anxiety on the blood pressure and how such an emotional response can counteract the effect of a drug. I have long had the fantasy that a department of psychiatry in a medical school would probably function most effectively if for 5 or 10 years it had no direct contact with any of the students but spent its teaching time with the members of the faculty. Even such fantasies may someday be possible of realization.

In order to integrate what we call the psychosomatic viewpoint into medicine eventually this type of teaching will have to begin in the medical school if not earlier. The next level which is not quite as satisfactory but presents some possibilities is the residency training in general hospitals, and this can be accomplished in many ways but particularly through the organization of psychiatry services in general hospitals. Our own service at The Mount Sinai Hospital is well known to most of you who are members of the staff, and you are also

familiar with the basic philosophy of this service. We are trying to become part and parcel of the total practice of medicine within the hospital. From this point of view perhaps the most important member of the staff is the liaison psychiatrist whose primary function is a teaching one, and this teaching has to take place at different levels. The most important contribution that he can make is in relation to the problems presented by the patient. At a practical level his psychiatric knowledge must prove of direct value to the physician or surgeon whose case is being dealt with. We have made a number of attempts, with varying success, to incorporate this point of view into the practice of all members of the staff. We have a long way to go. Nevertheless, at a pragmatic level an appreciation of the point of view has increased.

I have referred above to the psychoanalytic clarification of transference phenomena and have stated that this is related specifically to the art of the practice of medicine. It becomes possible to understand the patient-physician—the physician-patient relationship and to communicate this knowledge at all levels of training and practice. This contribution in itself, even if it were the only one that has been made, would have tremendous significance for medicine.

A word on the title of this paper. There are some who object to the term psychosomatic since it seems to imply a duality which does not exist. There may be some merit in this objection. On the other hand there is a possibility of a semantic quibbling. The important matter is the basic conceptual framework rather than the term. In view of this I should like to emphasize that there is not and never can be a speciality of psychosomatic medicine since all medicine is always by definition psychosomatic. There are implications in this point of view for psychotherapy, since it is clearly demonstrated that psychotherapy of necessity has to be a medical discipline even at its most pragmatic level.

I have tried in this brief and somewhat summary fashion to demonstrate the necessity and the feasibility for an integrated science of medicine based on a broad biologically oriented basis and to emphasize the practical significance for such a point of view in all areas of medicine—in its philosophy, in research and, perhaps of major significance to this audience, in the everyday practice of the art of medicine.

REFERENCES

1. BRUCH, HILDE: The Psychosomatic Aspects of Obesity. *J. Mt. Sinai Hosp.*, in press.
2. DEUTSCH, FELIX M., KAUFMAN, M. RALPH, AND BLUMGART, HERMAN L.: Present Methods of Teaching. *Psychosomatic Med.*, 2: 214, 1940.
3. HINKLE, LAWRENCE E., JR.: A Summary of Experimental Evidence Relating to Diabetes Mellitus. *J. Mt. Sinai Hosp.*, in press.
4. JANOWITZ, HENRY D., ET AL: A Quantitative Study of the Gastric Secretory Response to Sham Feeding in a Human Subject. *Gastroenterology*, 16: 104, 1950.
5. LEVINE, MAURICE: The Essence of Psychotherapy, presented in series of lectures on Recent Advances in Psychosomatic Medicine, held at The Mt. Sinai Hospital, January 9, 1952.
6. LIDZ, THEODORE: Emotional Factors in the Etiology and Treatment of Hyperthyroidism. *J. Mt. Sinai Hosp.*, in press.
7. MARGOLIN, SYDNEY G.: Psychophysiological Studies of Fistulous Openings into the Gastrointestinal Tract. *J. Mt. Sinai Hosp.*, in press.

8. ———, ET AL: Variations of Gastric Functions During Conscious and Unconscious Conflict States, Life Stress and Bodily Disease. 1950. Vol. 29 of the 1949 Proceedings Association for Research in Nervous and Mental Disease, p. 656.
9. ——— AND KAUFMAN, M. RALPH: What is Psychosomatic Medicine. The Medical Clinics of North America, New York Number, 32: 611, 1948.
10. MASSERMAN, JULES H.: Experimental Approaches to Psychosomatic Problems. J. Mt. Sinai Hosp., in press.
11. MIRSKY, I. ARTHUR, ET AL: Pepsinogen Excretion (Uropepsin) as an Index of the Influence of Various Life Situations on Gastric Secretions. Life Stress and Bodily Disease. 1950. Vol. 29 of the 1949 Proceedings Association for Research in Nervous and Mental Disease, p. 628.
12. PENFIELD, WILDER: Memory Mechanisms. Arch. of Neurol. & Psychiat., 67: 178, 1952.
13. PERSKY, HAROLD, GRINKER, ROY R., MIRSKY, I. ARTHUR, AND GAMM, STANFORD R.: Life Situations, Emotions and the Excretion of Hippuric Acid in Anxiety States. Life Stress and Bodily Disease. 1950. Vol. 29 of the 1949 Proceedings Association for Research in Nervous and Mental Disease, p. 297.
14. SHERRINGTON, SIR CHARLES: Man on his Nature. The Gifford Lectures, ed. 2, Cambridge, The University Press, 1951.
15. SIGERIST, HENRY E.: A History of Medicine. Vol. 1. Primitive and Archiac Medicine. New York, Oxford University Press, 1951.
16. WEISS, EDWARD: The Emotional Problems of Hypertension, presented in series of lectures on Recent Advances in Psychosomatic Medicine held at The Mount Sinai Hospital, March 26, 1952.

ACCESSORY LUNG—UNUSUAL VARIATIONS*†

GABRIEL P. SELEY, M.D.

New York

Accessory lung can occur in several different locations in the thorax, and the pathological anatomy varies widely. One of the types recently encountered consisted of a large systemic artery, partial "sequestration" of the accessory lung and a cystic cavity which communicated with a large bronchus. Cough and expectoration which are the chief symptoms in this variant are the result of infection in the accessory lung which has a free bronchial communication.

The following cases illustrate 2 other unusual variations of this condition.

The first case, C. C. (#608758) was an 8 year old female whose chief complaint was a non-productive cough of 3 months duration. A roentgenogram 2 weeks prior to admission revealed a "mediastinal tumor". Physical examination was entirely negative. X-ray examination showed a homogeneous soft tissue middle mediastinal density extending one inch to the left of the spine (Fig. 1). Operation was performed on March 14, 1950 by Drs. Nuehof and Seley.

Operation: Excision of accessory lung.

Findings and Procedure: The left chest was entered by a posterolateral incision through the fifth intercostal space. The fourth rib was divided close to the spine, and the ribs separated with a rib spreader. The lung was completely free of adhesions and no fluid was present in the pleural cavity. Situated in the mid-mediastinum was a yellow cystic mass measuring 5 x 3 cm., and attached to it was a small lappet of lung measuring 1 x 2 cm. The mass appeared to arise from the middle mediastinum in the region of the ascending aorta whose pulsations were reflected by the mass. The actual origin was from the mediastinal pleura in the region of the hilus of the lung along the ascending aorta about 3-4 cm. from the heart. There was no attachment to the lung. The blood supply came directly from the aorta via a narrow pedicle. The latter was divided between clamps and the mass excised. In suturing the pedicle, cartilage was encountered at one point. There was, however, no apparent connection with the tracheo-bronchial tree. The chest was closed in layers after reuniting the intercostal muscles, and the ribs were realigned with the Bailey approximator without the use of pericostal sutures. Penicillin (300,000 units) was instilled into the pleural cavity, the lung inflated, and the excess air removed by catheter. Silk sutures were used throughout. The post-operative course was entirely satisfactory and child has remained well.

Pathological Diagnosis (#P47726): "Partially cystic Neben Lunge. Cyst lined by ciliated epithelium. Specimen is an unfixed oval flat mass with a maximum diameter of 6.5 cm. and a lesser diameter of 3.5 cm. It is about 3 mm. long and is covered by a smooth glistening capsule. It has a definite appendage resembling

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† From the Department of Surgery, The Mount Sinai Hospital, New York, N. Y.

either thymic tissue or collapsed lung at one portion which shows some delicate fibrous lobulations. The entire surface is rather evenly congested but there is no obvious ruptured vessel. At one portion of the surface there is an agglomerate of small blood vessels and rather firm fibrous structures which resemble cartilage. When opened, about 30 cc. of creamy mucus are found in the cavity. The wall is 2-3 mm. thick and shows fibrous trabeculations which project about 1 mm. into the lumen. The lining is otherwise smooth, vaguely resembling bronchial mucosa. Teratoid structures are not found."

The second case, M. M., (# 608205) was a 41-year old white female who entered the Mount Sinai Hospital because of cough of 8 months duration. Six months prior to admission she was said to have "virus pneumonia" and 3 months later a lesion was noted in the paravertebral region of the right lower lobe. Bronchography failed to show filling in this area. Bronchoscopy on December 4, 1949 was negative except for slight fulness of the postero-lateral wall of the right lower

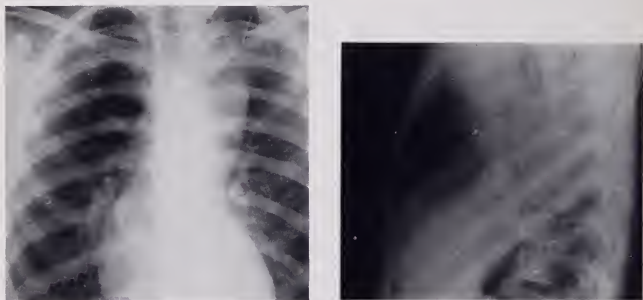


FIG. 1. Patient C. C. Postero-anterior and lateral roentgenograms of the chest showing a midmediastinal soft tissue density extending to the left of the spine.

lobe. Repeat bronchoscopy one month later was essentially negative. Biopsy specimens taken at that time were reported as showing "slight acute and chronic non-specific inflammation". A roentgenogram on March 1, 1950 (Fig. 2) showed "atelectasis with infiltration of mesial portion of the right lower lobe and a nodular type of infiltration near the root of the lung". Bronchography (Fig. 3) revealed no filling of the mesial division of the right lower lobe.

The diagnosis of adenoma or carcinoma was considered and an operation was performed on March 4, 1950 by Dr. Arthur Aufses. The chest was entered through a posterior approach and a well localized inflammatory lesion was encountered in the mesial portion of the right lower lobe. A large artery, $\frac{3}{8}$ " in diameter, was seen arising from the aorta 1 inch above the diaphragm and entered the lower lobe. The artery was ligated and lobectomy was performed in the usual manner. The post-operative course was entirely satisfactory and when last seen on October 16, 1951 the patient was entirely well. The chest x-ray taken at that time is shown in figure 4.

Pathological Report (#014498): "Aberrant arterial branch (from aorta) to portion of right lower lobe of lung with saccular bronchiectasis and acute and chronic pneumonitis of above segment. Fluid injected into artery exudes from main pulmonary vein branch but direct communication was not ascertained. No accessory bronchus present."

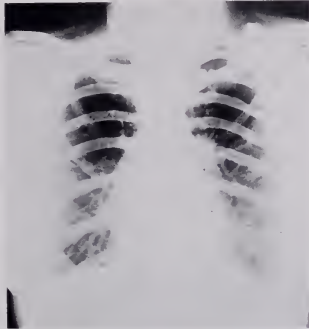


FIG. 2. Patient M. M. Roentgenogram of the chest showing atelectasis with infiltration of the medial portion of the right lower lobe and a nodular infiltration in the region of the right hilus.



FIG. 3. Patient M. M. Bronchogram which reveals no filling of the medial division of the right lower lobe.

The first case is most unusual because it is the first recorded instance of an accessory lung situated in the supra-hilar area receiving an artery from the aorta and showing evidence of cystic disease. In a recent article, Cole, Alley and Jones (1) state that in all the cases to date there was not a single instance of an anomalous systemic artery to the lung in the supra-hilar area associated with anomaly of the lung. This case had not only cystic disease of the accessory lung, but complete sequestration. The second case is an example of an accessory lung without sequestration but with lung infection and a systemic artery to the lung.

It is apparent from these cases that there are many varieties of accessory lung. In the last few years numerous reports have appeared on this subject. DeBakey, Arey and Brunazzi (2) reported the successful removal of a lower accessory lobe in a 7-year old Negro female. They mention the association of accessory lung with diaphragmatic defects and stress the preponderance of left-sided accessory lungs. Leahy and MacCallum (3) reported a 36-year old female who had a left-sided cystic accessory lobe in the region of the pulmonary ligament that simulated a thin-walled cyst the size of a fetal head. Brewer, Claggett and MacDonald (4) discussed the subject of anomalous arteries to the lung associated with congenital pulmonary abnormality. They included a detailed description of the embryology of this anomaly as follows: "There is a capillary plexus which embraces the primitive gut and the region of the fore-gut where the pulmonary anlage develops is of special interest. The whole plexus is the splanchnic plexus and is connected with the aorta. The lung bud carries part of the splanchnic plexus with it and becomes the post-bronchial pulmonary plexus. The pulmonary

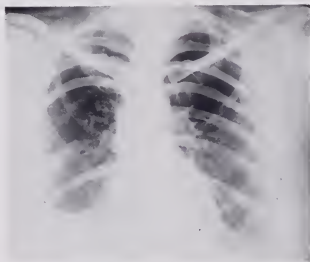


FIG. 4. Patient M. M. Post-operative roentgenogram of the chest

arteries which start as angioblastic buds from the aortic sac inosculate with the plexus on the lung bud and the connection with the dorsal aorta atrophies. If this connection persists, then abnormal arteries are present. If the sequestration takes place in the 4 mm. stage agenesis of the lung takes place. If the sequestration occurs at 14 mm. stage only a lobe or portion of a lobe is affected." Pryce (5) was the first to postulate the "sequestration" theory. He suggests that an aberrant artery captures one or more bulbous tips of the developing lung bud. Then sequestration (dissociation) or death of "captured" primitive pulmonary tissue takes place, resulting in congenital cysts, lower accessory lung, or pulmonary agenesis, depending on the size of the lung bud.

Infection in a "sequestered" lung may occur either (a) through communication with the bronchial tree, (b) by hematogenous infection or (c) from the adjacent normal lung.

Brewer, Claggett and MacDonald (4) report 18 cases on the left, 10 on the right, and one bilateral whereas DeBakey, Arey, and Brunazzi (2) stress the

preponderance of left-sided accessory lungs. The abnormality in the second case herein presented is on the right side. The changes in the artery are frequent and histologically simulate a pulmonary artery. The anomalous vessel is often sclerotic. The changes in the vessel wall may be due to endarteritis resulting from non-function, infection, or pressure which is high since it comes directly from the aorta. However, the fact that this anomalous vessel *does not have the capillary bed to take up the pressure* has not been stressed and probably represents the chief mechanism in the production of sclerosis which is found even in very young individuals. The presence of an anomalous vessel which contains blood under high pressure and whose wall is sclerotic presents a hazard when the surgeon does not suspect, or is not aware of, the presence of one of these anomalous vessels. One should be alert to this possibility in all lower lobe lobectomies, especially those performed for suppurative disease.

Another interesting abnormality is that of an anomalous lobe of lung arising from the esophagus. Gans and Potts (6) report a 5-months old female who presented such an abnormality in the apex of the left chest. Since the esophagus and trachea are originally one structure, the early gut has respiratory potentialities and this anomaly can occur. Tracheo-esophageal fistula, a more common anomaly, represents an incomplete separation of the laryngotracheal groove from the gut.

Cole, Alley, and Jones (1) state that anomalous systemic arteries to the lung have originated from the aorta and all its major branches, both thoracic and upper abdominal. They agree with the classification of Finley and Maier (7) who divide these vessels into supra-hilar (37.3 %) and infra-hilar (62.7 %). The supra-hilar vessels are often (75 %) associated with major anomalies of the heart and great vessels. However, Cole *et al* (2) state that none of these latter were associated with anomalies of the lungs. The first case is an example of a supra-hilar anomalous vessel associated with a completely sequestered cystic lung. It is therefore of great interest as it is the first recorded instance of this anomaly.

Of the present theories explaining the pathogenesis of accessory lung, the most plausible seems to be that of Cole, Alley and Jones (2), who state that there is an interference with the embryonic organization in the lower chest behind the heart involving the lower pulmonary tissue, posterior portion of diaphragm and the remaining communicating small vessels between the old pulmonary plexus in the dorsal aortic zone. Although this does not explain the first case, it offers a satisfactory pathogenesis for most of the cases encountered. The term "lower" and "left" should be omitted from the nomenclature and "accessory lung" used to cover all these anomalies whether they occur in the lower or upper chest, right or left side, and regardless of the degree of sequestration.

REFERENCES

1. COLE, F. H., ALLEY, F. H., AND JONES, R. S.: Aberrant Systemic Arteries to the Lower Lung. Surg., Gynec. & Obst., 93: 589, 1951.
2. DEBAKEY, M., AREY, J. B., AND BRUNAZZI, R.: Removal of Lower Accessory Lobe. J. Thor. Surg., 19: 304, 1950.
3. LEAHY, L. J., AND MACCALLUM, J. D.: Cystic Accessory Lobe Left. J. Thor. Surg., 20: 72, 1950.

4. BREWER, A., CLAGETT, O., AND MACDONALD, J. R.: Anomalous Arteries to the Lung Associated With Congenital Pulmonary Abnormalities. *J. Thor. Surg.*, 19: 957, 1950.
5. PRYCE, D. M.: Lower Accessory Pulmonary Artery With Intra-lobar Sequestration of Lung: A Report of Seven Cases. *J. Path. & Bact.*, 58: 457, 1946.
6. GANS, S. L., AND POTTS, W. J.: Anomalous Lobe of Lung Arising from the Esophagus. *J. Thor. Surg.*, 21: 213, 1951.
7. FINLEY, C. W., AND MAIER, H. C.: Anomalies of the Pulmonary Artery and Their Surgical Significance. *Surg.*, 29: 604, 1951.

AFIBRINOGENEMIA IN PREGNANCY: DIAGNOSIS AND TREATMENT*

HERBERT CHESSIN, M.D., AND J. CONRAD GREENWALD, M.D.

New York, N. Y.

The recent obstetrical literature contains an increasing number of references to afibrinogenemia or intra-vascular defibrination associated with pregnancy. DeLee (1), in 1901, reported the failure of the blood to clot in a patient with abruptio placenta; a similar observation was made by Williams (2) in 1915. Dieckman (3), in 1936, was the first to demonstrate that decreased fibrinogen concentration was responsible for the coagulation defect in some cases of abruptio placenta. In 1949, Moloney (4) reported the use of intravenous fibrinogen and whole blood in the treatment of a coagulation defect due to fibrinogen deficiency. Weiner and associates (5, 6) also report afibrinogenemia in patients with abruptio placenta, and in several sensitized Rh-negative patients who had retained a dead fetus in utero for a prolonged period.

A case of afibrinogenemia was recently treated on the obstetrical service of The Mount Sinai Hospital.

CASE REPORT

Mrs. M. W. was a 27-year-old, colored, para 2-0-1-2 with an expected date of confinement of February 23, 1953. In 1942 and 1944, she had had full-term deliveries, the second of which was followed by immediate post-partum bleeding requiring temporary uterine tamponade, but no transfusion. In 1950 a dilatation and curettage was done following a spontaneous abortion during the third month of pregnancy. The patient was first seen in the prenatal clinic of The Mount Sinai Hospital in the 25th week of gestation at which time she had normal physical and laboratory findings. Her blood type was O, Rh-positive. During the 33rd week, the blood pressure rose to 140/90 and remained at that level until admission to the hospital. Edema, albuminuria, excessive weight gain and abnormal blood chemical findings were not present during her prenatal course. However, an eye ground examination during the 37th week revealed an increase in the light reflex, slight narrowing of the arteries, and localized areas of arteriolar spasm.

In view of the persistence of the increase in blood pressure, the patient was admitted to the hospital 12 days before term for induction of labor. The membranes were stripped digitally and a dilute solution of pitocin was administered intravenously. The blood pressure at this time was 140/90 and during labor it ranged between 135/85 and 140/90. General sedation was given during the first stage of labor during which a total of .25 cc. of pitocin was given. After a 4 hour first stage, the membranes ruptured spontaneously and clear amniotic fluid drained forth. Following a 30-minute second stage, the patient was delivered of a 3700 gram normal infant with the aid of outlet forceps over a median episiotomy. Anesthesia was produced with cyclopropane, nitrous oxide and oxygen. Two minutes after birth the placenta separated and was delivered intact by means of fundal pressure. No gross evidence of any abnormality of the placenta was seen; there was no retroplacental blood clot, nor placental infarct. Intramuscular ergotrate was given and the intravenous

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From the Department of Obstetrics and Gynecology, The Mount Sinai Hospital, New York City.

pitocin drip was continued. During the surgical repair of the episiotomy an excessive amount of bright blood flowed from the vagina. The uterus was carefully palpated and found to be firm and well contracted. The vagina and cervix were carefully inspected and a small cervical laceration was noted as well as several abrasions of the vagina; but there was no active bleeding from these small wounds. The repair of the episiotomy was continued, and a transfusion of 1000 cc. of whole blood was started. Uterine bleeding persisted despite the firm fundus and the administration of oxytocics. At this time, the cervical laceration and the vaginal abrasions were sutured to assure hemostasis.

It was noted at this point, 1 hour and 15 minutes post-delivery, that the blood which had collected in the waste pan remained fluid with no evidence of clot formation, and that the repaired episiotomy was oozing. Venous blood drawn to determine clotting time did not form a clot. A second 1000 cc. of whole blood was started and consultation with the department of hematology confirmed the diagnosis of afibrinogenemia. Two hours and 15

TABLE I
Fibrinogen determinations in the case of Mrs. M. W.

DATE	TIME		FIBRINOGEN LEVEL*	CLOTTING TIME
			mgms %	
2/12/53	6:45 P.M.	Delivery of placenta		
	7:00-8:00 P.M.	1000 cc. blood transfusion		
	8:00 P.M.	Blood sample†	150	No clotting
	8:00-11:00 P.M.	1500 cc. blood transfusion		
	9:00 P.M.	3 grams fibrinogen i.v.		
	9:25 P.M.	Blood sample†	280	10 min. 50% lysed in 30 min. 75% lysed in 24 hrs.
	10:45 P.M.	Blood sample	320	7 min. 10% lysed in 24 hrs.
2/13/53	1:00 A.M.	Blood sample	350	7 min. No lysis in 24 hrs.
	11:30 A.M.	Blood sample	360	5.5 min.
2/18/53		Blood sample	420	
		Blood sample		

* Normal fibrinogen levels at this stage of pregnancy range between 300-500 mgms%.

† A fibrinolysin was found to be present in these samples.

minutes after delivery, 3 grams of fibrinogen were given intravenously. Within 25 minutes, the uterine bleeding had decreased to a slight trickle with clot formation and a venous blood sample taken at this time revealed a 10-minute clotting time. Four hours after delivery, the bleeding had ceased, and the blood pressure, which had fallen to 90/60 during the bleeding phase, returned to 130/80. Blood loss was estimated at 2000 cc. and the patient was given a total of 2500 cc. of whole blood to compensate for it. Complete blood counts, including platelet determination, were normal during the height of the bleeding as well as in the later puerperium. Prothrombin time was slightly prolonged during the bleeding phase, but normal thereafter. Urine examination, chest x-ray, and EKG (the two latter taken to rule out the possibility of fibrin emboli) were also normal. The patient's later post-partum course was uneventful, except for a moderate thrombophlebitis of the wrist at the site of venipuncture.

Table I presents a summary of the fibrinogen determinations.

DISCUSSION

Two major theories have been proposed to explain the syndrome of afibrinogenemia. One (4, 5) claims that a fibrinolytic enzyme enters the maternal sinusoids from necrotic decidua and then destroys the circulating fibrinogen; the other (7, 8, 9, 10, 11) suggests that thromboplastic material from the placenta or amniotic fluid gains access to the maternal circulation, causing a marked disseminated intravascular coagulation with resultant defibrination of the blood. It has been shown that focal coagulation (8, 9, 11) can cause fibrin clots to form emboli with infarction and death. However, in view of the vast capillary bed defibrination is generally so disseminated that symptomatic emboli do not occur. Weiner (6) has suggested that afibrinogenemia is the result of depressed fibrinogen production by the liver due to some toxic fetal or maternal substance. No evidence has been adduced to support this theory.

Regardless of etiology, the obstetrician must quickly diagnose the presence of this coagulation defect and remedy it before exsanguination takes place. Afibrinogenemia usually occurs in patients who have toxemia of pregnancy with hypertension, abruptio placenta, amniotic fluid (12) "infusion," or a long-standing fetal death in utero (most commonly in Rh-negative sensitized women). The appearance of ecchymoses, bleeding from the gums, venipuncture sites, or a well-sutured episiotomy should suggest this condition, especially in the presence of a negative tourniquet test.

Observations of the size and stability of the clot formed in a sample of uncitrated venous blood in a test tube or bottle is the most practical diagnostic test. In the normal patient the clot that forms is large, resists shaking, binds the majority of the red cells, and is stable after incubation at 37°C. for at least 24 hours. When plasma fibrinogen is low, initial clotting may occur but fragmentation can take place within a few minutes. As a practical matter, if the patient's incubated venous blood clot is stable for one hour, enough fibrinogen is present for adequate hemostasis (5). This test is important not only in the recognition of this condition, but it will serve as an index in evaluating the result of fibrinogen therapy. Laboratory assay of the fibrinogen concentration is, of course, the ideal diagnostic procedure; but it is time consuming, requiring many hours.

The blood loss which these patients suffer may be severe. Experience has shown that it is sometimes impossible to administer whole blood at a rate rapid enough to increase the blood fibrinogen concentration to effective coagulant levels. One bottle of blood may raise the fibrinogen level by only 10 mgm % (6). Blood replacement is necessary, but fibrinogen administration is the only effective method, short of complete replacement of the entire circulating blood volume, to produce normal coagulation and hemostasis in these desperate cases. The minimum effective amount necessary to control the hemorrhage varies. In our patient the initial dose of 3 grams of fibrinogen was sufficient. However, the total amount necessary may be more than 15 grams. It is necessary to determine the patient's clotting time and the stability of the clot for several hours during and after therapy to insure maintenance of adequate fibrinogen levels. It often becomes necessary to repeat the intravenous administration of fibrinogen.

What part does hysterectomy play in the treatment of this syndrome? Clinical experience has shown that the usual methods of surgical hemostasis should be avoided until the coagulation mechanism has been restored to normal. When the fibrinogen level reaches the normal range and blood replacement has been accomplished, surgery is almost never necessary.

SUMMARY

1. A case of afibrinogenemia in a patient with a very mild hypertensive toxemia of pregnancy has been presented.
2. The history, theories of etiology, diagnosis and treatment of this coagulation defect have been briefly reviewed.
3. Prompt recognition and adequate therapy of afibrinogenemia may prevent an obstetrical catastrophe.

REFERENCES

1. DELEE, J. B.: Case of Fatal Hemorrhagic Diathesis with Premature Detachment of Placenta. *Am. J. Obst.*, 44: 785, 1901.
2. WILLIAMS, J. W.: Premature Separation of the Normally Implanted Placenta. *Surg. Gynec. & Obst.*, 21: 541, 1915.
3. DIECKMANN, W. J.: Blood Chemistry and Renal Function in Abruptio Placentae. *Am. J. Obst. & Gynec.*, 31: 734, 1936.
4. MOLONEY, W. C., EGAN, W. J., AND GORMAN, A. J.: Acquired Afibrinogenemia in Pregnancy. *New England J. of Med.*, 240: 596, 1949.
5. WEINER, A. E., REID, D. E., AND ROBY, C. C.: Coagulation Defects Associated with Premature Separation of the Normally Implanted Placenta. *Am. J. Obst. & Gynec.*, 60: 379, 1950.
6. WEINER, A. E., REID, D. E., ROBY, C. C., AND DIAMOND, L. K.: Coagulation Defects with Intrauterine Death from Rh Isosensitization. *Am. J. Obst. & Gynec.*, 60: 1015, 1950.
7. PAGE, E. W., FULTON, L. D., AND GLENDENING, M. B.: The Cause of the Blood Coagulation Defect Following Abruptio Placentae. *Am. J. Obst. & Gynec.*, 61: 1116, 1951.
8. SCHNEIDER, C. L.: "Fibrin Embolism" (Disseminated Intravascular Coagulation) with Defibrination as one of the End Results During Placenta Abruptio. *Surg. Gynec. & Obst.*, 92: 27, 1951.
9. SCHNEIDER, C. L.: Complications of Late Pregnancy in Rabbits Induced by Experimental Placental Trauma. *Surg. Gynec. & Obst.*, 90: 613, 1950.
10. SCHNEIDER, C. L.: Abruptio Placentae after Fetal Death in Utero. *Obst. & Gynec.*, 1: 321, 1953.
11. WEBER, L. L., MERANZE, D. R., AND KAPLAN, F.: Intravascular Clotting Complications of Pregnancy. *Am. J. Obst. & Gynec.*, 64: 1037, 1952.
12. REID, D. E., WEINER, A. E., AND ROBY, C. C.: Presumptive Amniotic Fluid Infusion with Resultant Postpartum Hemorrhage Due to Afibrinogenemia. *J.A.M.A.*, 152: 227, 1953.

SOME GYNECOLOGICAL IMPLICATIONS OF THE CASTRATION COMPLEX*

BERNARD C. MEYER, M.D.

Macbeth: How does your patient, doctor?

Doctor: Not so sick, my lord,
As she is troubled with thick coming fancies,
That keep her from her rest.

Macbeth: Cure her of that:
Canst thou not minister to a mind diseased,
Pluck from the memory a rooted sorrow,
Rage out the written troubles of the brain,
And with some sweet oblivious antidote
Cleanse the stuff'd bosom of that perilous stuff
Which weighs upon the heart?

In this presentation the term *castration* is used not in the biologic but in the psychoanalytic sense, referring to conscious or unconscious ideations of genital mutilation or to its symbolic equivalent (1, 2). The observation by children of the anatomical differences between the sexes is often interpreted by them to indicate that the female has lost her penis or has not yet grown one, and that the male incurs the danger of losing his (1). Such notions contribute to a number of unconscious pathogenic attitudes which persist into adult life despite an intellectual awareness of their falseness. Thus the absence of a penis may create a chronic sense of major deprivation throughout the life of a woman together with an unremitting sense of envy and covetousness of the penis of the better equipped man. Yet the importance to the girl of her lack of penis is in large measure dependent upon her basic sense of security and acceptance. A little girl who feels cherished and loved by both parents can regard her lack of penis more as an anatomical phenomenon than as a badge of inferiority or brand of discrimination. Her knowledge that she will bear children which her brother cannot do provides her with compensations for her apparent incompleteness. On the other hand, the girl who feels rejected may well regard her lack of penis both as a sign of that rejection and as the defect which renders her less acceptable to her parents than are her brothers. To her the lack of penis symbolizes lack of love, for which defect she may hold one or both of her parents responsible. As she grows older several significant biologic and psychologic events will reveal the firm impress of this sense of being mutilated. In many women, however, the hope of having a child continues to serve as a compensation for being "mutilated" so that in an unconscious and symbolic sense to become pregnant means to have acquired a penis. In the mind of the little girl it is most often from the father that she hopes to be given this child. In other instances the rejection of femininity is so strong that the compensation of childbearing offers no solace, and such women may go through life hoping and despairing of the hope that a miracle will one day find them anatomically "perfect". Indeed in many psychoanalyses it is evident that

* From the Department of Psychiatry, The Mount Sinai Hospital, New York City.

the development of a penis or the achievement of pregnancy constitutes the unconscious criterion of "cure" (2). With each successive menstrual period there may occur periodic outbursts of dissatisfaction with the therapist or the therapy coupled with threats of quitting, or going to another doctor, or undertaking a different type of treatment. In fact, the analyst may often correctly suspect that menstruation is at hand from just such utterances.

The woman who feels castrated engages in a variety of attitudes to help her cope with the situation. Her attitude toward her body may be one of distaste or violent revulsion. All reminders of her sex may prove hateful. Conversely, she may endeavor to deny her sense of mutilation by over-valuing other portions of her body, such as her hair, her breasts, or her body in its entirety. Spectacular and flamboyant clothes and hats as well as extraordinary feats of physical skill may serve to deny that she is physically defective, a denial which assumes the unconscious formulation that now the entire body has become the penis (3). As its most striking expression of the "phallic" woman stands the ballerina, a veritable bird in flight, who surrounded by degraded (castrated) males, dances on the tips of her toes and leaps through the air with a grace and perfection which serve as a poetic denial of any thought of mutilation. In the words of Agnes De Mille, dancer and choreographer, "The very physical stresses, the strengthening and bracing and tautening of her back and leg supply such a sense of driving power as to give her the illusion of male potency" (4). In other women in whom such gifts are less available other forms of compensation are sought for. Such women may feel that they can do anything a man can do, as a consequence of which they may display pseudo-masculine behavior and manners, driving ambition, intellectual pretentiousness and so forth. Such women not infrequently may champion for "sexual equality". A woman undergoing analysis came to a session wearing a man's trousers, motorcyclist's goggles and a trapper's hat. "Things are going pretty well," she began, and then, making a slip of the tongue, added, "There is just one ointment in the fly." In other instances the sense of having a penis may be achieved by regarding the male in the environment as well as his penis as a mere physical extension of herself. Thus the same woman, married to a man nine years her junior ordered him to have intercourse with her in the following manner: for about twenty minutes after inserting his penis he was not to move whatever, during which interval she would try to imagine that the penis was really attached to her. She never uncovered her breasts nor allowed them to be played with.

Iras: *Am I not an inch of fortune better than she?*

Charmian: *Well, if you were but an inch of fortune better than I
 where would you choose it?*

Iras: *Not in my husband's nose.*

(Antony and Cleopatra)

Obviously women who regard themselves as mutilated humans and who harbour deep feelings of resentment and covetousness toward the penis cannot be expected to respond well to coitus which then tends to be evaluated as further humiliation and degradation. That which should be undertaken with joy and

abandon becomes instead a vehicle for intense anxiety, rage and resentment, leading inevitably to a variety of sexual disturbances, frigidity, quarrels and tears. One woman who went into the bathroom to weep after each coitus, observed, however, that this reaction (to the "humiliation") was less likely to occur if earlier during the same day she had achieved some sense of significant personal success. During his love making, moreover, she often annoyed and exasperated her husband by giggling. Resentment toward the penis was expressed in a more symbolic manner by another lady who was undergoing psychoanalysis. A few nights after her husband presented her with a fountain pen for Christmas she had the following dream: *She was very angry about this same pen and hurled it across the room, causing ink to splatter all over her pretty newly covered sofa. Her husband burst into tears, whereupon she felt remorseful and apologized.* Concluding the recital of this dream she burst out angrily against her husband, demanding to know why he didn't leave her alone and allow her to write with pen holder and ink, knowing as he did that she disliked fountain pens. When she then asked, "What does all this mean, doctor?" I replied that it seemed to me that the degree of emotional disturbance was out of proportion to her having received a fountain pen from her husband and that consequently I suspected that the entire subject contained a hidden and deeper significance for her. "I don't know," she said, "All I can think of is Gertrude Stein: A pen-is-a-pen-is-a-pen-is-a-pen." I asked her "How do you spell that?" For a moment she was silent; then, "I get it."

Other women combat the sense of degradation by selecting as mates men whose sole "advantage" over them would appear to be their possession of a penis, that is, men who are younger, shorter, weaker, poorer, sick, crippled, or from an inferior social level. In addition they may choose men of fragile potency whose sexual effectiveness is largely a matter of her management, enabling her to conclude that he is a man only by grace of her. Such a woman avoids and often detests men she feels she cannot control. Thus Katharine speaks at the close of the *Taming of the Shrew*:

*I am ashamed that women are so simple
To offer war when they should kneel for peace,
Or seek to rule, supremacy, and sway,
When they are bound to serve, love and obey.
Why are our bodies soft and weak and smooth,
Unapt to toil and trouble in the world,
But that our soft conditions and our hearts
Should well agree with our external parts?*

Pregnancy. Attitudes to pregnancy range from a woman's feeling of complete fulfillment and bliss to violent rages at the enslavement which such a state subjects her to. The condition of pregnancy may be accompanied by a manifestation of sweetness and contentedness which has never before been evident, as if a life-long hope had met with realization. Subsequent to delivery, however, the mood may revert to its former picture, indicating that in some women, at least, the wish to be pregnant is not necessarily identical with the wish to be a mother. In fact the birth of a child may be construed as a loss, and as such a repetition

of the "original mutilation". In some instances the birth of a son is construed as a sign of the mother's masculinity. Such mothers may react to the birth of a daughter with shock and ill-concealed disappointment, as if they had never even counted on the possibility of such a disaster. Thus when one woman was told by the nurse that a little girl had been born the new mother snapped back, "Don't be funny!" When she finally realized that this was indeed true she moaned, "Take it away," and turned her face to the wall. Five weeks later she abandoned both daughter and husband. Boys born of such a mother tend to remain her phallic appendage; their capacity to function as autonomous individuals is severely crippled. One mother who referred to her son as a "second Edison" claimed to be so close to him that they both experienced mutually telepathic dreams.

Breasts. Whereas most women tend to attach considerable feelings of pride to the breasts, women who feel genitally mutilated are prone either to over-value them as compensation for the lack of penis, or despise them as an unwanted reminder of their sex. The latter derive no real pleasure from having their breasts praised or fondled and may endeavor to conceal them as far as possible. When an excessive narcissistic value is placed on the breasts nursing may be avoided lest they lose their attractiveness. In other instances and for comparable reasons a mother may make an exhibitionistic show of nursing her baby, as if to challenge her husband and others with the query: "Can *you* do it?"

Removal of a breast constitutes a severe trauma to virtually all women and evokes regularly a psychic reaction which is akin to mourning. Yet the intensity and duration of such reactions show considerable variation depending upon both the personality of the individual and her life experiences. Obviously to a young and childless woman the loss of a breast will have a far different meaning than to a woman in the post-climacterium who has successfully reared a family. In general one may assert that the more successfully a woman has realized her feminine creative endowments the better she will tolerate the loss of the prized breast. A 48 year old childless woman was seen in psychiatric consultation prior to mastectomy for cancer. During the interview when the subject of children was mentioned she began to weep indicating that her barrenness during twenty-five years of marriage had been a sore disappointment. The impression was gained that her impending mastectomy would spell the death blow to her frustrated hope to be a mother, and that would react to the operation with a depression. Two days after the procedure she spoke of suicide and a day later developed a most unexpected cerebral vascular accident resulting in an aphasia and hemiplegia affecting the side of the amputated breast. On the other hand, amputation of the breast takes on the character of a renewed castration especially in those women who regard the breast as a major compensation for the lack of penis. A post-mastectomy dream of one woman clearly indicated how she equated her lost breast to a masculine symbol. This patient had had three children; ten years before her operation she had lost her only son, a boy of nine. Two days after the mastectomy she dreamed that she was running after this boy who constantly eluded her outstretched grasp. When asked in which direction the boy was run-

ning, she replied, "To the left; always to the left." It was the left breast which had been removed.

In other instances long standing neurotic difficulties have created life situations which may be more or less tolerable until the occurrence of a "renewed" mutilating disaster such as a breast amputation or hysterectomy resulting in a violent psychic upheaval. I have in mind, for example, unmarried women who have remained immaturely and masochistically attached to a mother or sibling, all the while promising themselves that one day they will escape from their "servitude", the latter being often largely motivated by guilt. Mutilating operations performed upon such individuals may open the flood gates of pent up rage and sado-masochistic aggression to the end that a psychosis may ensue. Occasionally one encounters extraordinary efforts at denial of any emotional reaction whatever. Thus one lady past fifty, a Christian Scientist, had experienced two unsuccessful marriages, the second ending in her being abandoned by a repeatedly unfaithful husband. She had lost two sets of twins and was disowned by her sole remaining child. Six years prior to mastectomy she had undergone an oophorectomy for cancer. Following her breast amputation her sole emotional response to the procedure was to praise the surgeon's skill and the "beauty" of the incision. Yet during the night the nurses could hear her screaming. It goes without saying that a general awareness of the personality make-up as well as of the life experience of women being subjected to gynecologic surgery is essential to the total success of such an undertaking.

Menstruation. The onset of menstruation constitutes a major psychophysiologic event in the life of a girl. Her attitude toward its occurrence shows a wide variation, ranging from a joyful sense of having become a woman to a horror stricken feeling of fright, disgust and dirtiness. It is noteworthy how often the menarche occurs as a shocking experience despite evident foreknowledge of the phenomenon. Subsequent periods tend to be accompanied by mood changes comparable to those present at the time of the first period (5). Depression in association with the period may represent a disappointment in a woman desiring to be pregnant: "the weeping of the disappointed uterus." Thus one woman in describing her pre-menstrual depression said, "This always happens to me before I get pregnant—, I mean, my period." In addition to its indicating the absence of pregnancy, the flow of menstrual blood serves as a renewed proof of castration and inferiority, eliciting intense feelings of depression, irritability, rage, and sadistic or masochistic aggression. It is stated that most suicides among women occur at the time of the menses (6).

*From him it is that murder's thirst,
Blood lapping, inwardly is nursed—
Ere time the ancient scar can sain,
New blood comes welling forth again.*

(From Agamemnon of Aeschylus)

The popular terms applied to the menstrual period abundantly emphasize the emotional climate which pervades it. Brush (7) lists colloquialisms by which the

menses are referred to by some women. Included among them are the following, most of which emphasize illness or injury: falling off the roof, being sick, being unwell, being hit, going off, sprained ankle, the plague, tin can fever, red tummy ache, cutting, the pip, etc. Other terms carry a connotation of a ghoulish or death-like flavor: the curse, the visitor from the shore, the lady in waiting, etc. Still others underscore the sense of forced inactivity and isolation: the nuisance, the rag, riding a cotton bicycle, the Woman's Home Companion. Such expressions find their counterpart in the prejudices and taboos which are applied in many cultures to the menstruating woman. Chadwick (8) and Devereux (9) have stressed the close parallelism between the attitudes of primitive peoples toward menstruating women and those which have been directed against witches, for in both instances these attitudes reflect a belief in their malevolent influences. Thus a woman during her flux is to be avoided for she is judged capable of threatening a man's virility, causing a horse to break its leg, turning milk sour and wine to vinegar, blighting crops and causing mares to abort. Such ideas are derived in large measure from a recognition of the hostile aggression and penis envy of the periodically "castrated" woman as well as from a revival of the man's own castration anxiety when confronted by the bleeding female genital. Devereux (9) states that the pubescent Mohave Indian girl was forbidden to look at her image in the water or in a mirror under penalty of becoming cross-eyed, a taboo which is undoubtedly related to the primitive belief in the evil eye. A young woman observed by the writer expressed frequent fears of sudden blindness. She was subject, moreover, to transient states of hysterical amblyopia which terrified her. Although she enjoyed an active sexual relationship she had never looked at her partner's penis. She felt certain, moreover, that if she did look her vision would fail her. Tennyson describes the consequences of a violation of a taboo against looking when the Lady of Shalott espies in her mirror the approach of Sir Lancelot:

*She left the web she left the loom,
 She made three paces through the room
 She saw the water-lily bloom;
 She saw the helmet and the plume
 She look'd down to Camelot.
 Out flew the web and floated wide;
 The mirror crack'd from side to side:
 "The curse is come upon me" cried
 The Lady of Shalott.*

(Menses?)

In recognition of her sadistic aggression toward the penis during the "period" in some primitive societies the menstruating woman is forbidden to eat meat because of its cannibalistic import (9). The patient mentioned above, who feared blindness, and one other, to be described at the conclusion of this paper, spontaneously renounced meat during their flow, stating that the sight of it, especially if it were undercooked, produced nausea at such times. Neither of them was familiar with a meat taboo among primitive peoples. In addition such defenses

against an impulse to destroy or bite off the penis, other women display a pronounced tendency toward self-injury during the flux, indicating a turning of their aggressive impulses upon themselves. To this is undoubtedly related the custom wherein a mother slaps the face of her daughter at the time of the menarche (5). This gesture, allegedly performed for "good luck" finds its counterpart in initiation ceremonies among some primitive people (9). Unconsciously it may betoken the mother's resentment toward the bleeding female genital and a jealous reaction toward a prospective competitor.

Creon (to Medea): I fear thee—no longer need I veil my dread 'neath words—lest thou devise against my child some cureless ill. Many things contribute to this fear of mine; thou art a witch by nature, expert in countless sorceries, and thou art chafing for the loss of thy husband's affection.

Menstruation may be regarded with aversion and disgust for other reasons. In some girls it is taken as a punishment for masturbation, i.e. as a sign of sin. Still others regard it as a form of incontinence. Thus Brush (7) mentions one woman who referred to her menses as "number three", another type of excretion.

Whereas some degree of emotional disturbance is common in many women before or during the period, others boast that they are completely indifferent to the experience. Such attitudes may be found in women who strive vigorously to deny their femininity and all manifestations of it. Emotional reactions to the period show considerable variation, moreover, in the same individual, depending in large measure upon the influence of other factors upon their mood. Thus a happy girl may accept the advent of her period with far less emotional accompaniment than obtains when she feels defeated and unloved.

Whereas primary organic and anatomical factors are responsible for some instances of painful menstruation, it would appear that psychologic factors are probably the commonest cause of severe dysmenorrhea (10). As in the case of the mood changes accompanying menstruation, the degree of incapacity and suffering from menstrual cramps shows considerable variation from month to month in the same individual (5). Hypnosis has been successful in relieving dysmenorrhea in a number of instances (10). Moreover some of the relief achieved through mechanical measures and after childbirth would appear to be due to psychologic influences. A young woman treated by the writer had become free of most of her physical discomfort during the menses with the establishment of a happy love affair. Just before one of her periods, however, the analysis of a dream threatened to bring to her awareness her marked aggressive and sadistic attitudes toward men. The content of the dream indicated that she entertained castrating wishes toward both her lover and her analyst. During the period which immediately followed she was tortured by the most severe cramps she could recall and she was preoccupied by fears of self injury.

Whereas menstruation brings in its train a number of severe changes in emotional status, it is itself remarkably susceptible to psychic influence. Reider (11) described the onset of a delayed menarche in a fifteen year old girl after one psychotherapeutic interview. Amenorrhea, premature, and delayed menstua-

tion of psychogenic origin have been repeatedly described. Menstruation is often delayed in girls who fear they are pregnant, only to appear once they are told their fears are groundless. A woman of forty whose periods had been regular became amenorrheic over an interval of four months after her lover decided to terminate their affair. When four months later their sexual relation was resumed she began to bleed within one hour after coitus. Premature menstruation in brides is a common occurrence frustrating the careful plans which have been made in setting a wedding date which will not coincide with an expected period. Such honeymoon bleeding is generally accepted to indicate a fear of or an aversion to intercourse, (12) although Balint (13) believes that in some instances it may be motivated by a primitive wish to seduce and excite the man as well as to serve as a test of his love. Premature menstruation may also take place upon occasions when it threatens to interfere with that feeling of being at her best which a woman desires for carrying out her plans. When subjected to analytic investigation such plans often appear to contain latent sadistic or castrating components to defeat which the woman, so-to-speak, castrates herself. In the absence of psychologic insight she is apt to complain, "Just my luck!"

Menorrhagia and metrorrhagia of psychogenic origin have also been reported. Miller (14) reported a case of prolonged menstrual bleeding which ceased abruptly when the patient realized that the purpose of her constant flow was to prevent her from yielding to an extramarital temptation. The writer observed a young woman in analytic therapy over a number of years who experienced several episodes of sudden intermenstrual vaginal bleeding. Because of the bizarre character of these episodes and because the psychological features of the case serve to illustrate some of the foregoing material it will be presented in some detail.

One day while cleaning a chicken in the kitchen, Mary, a 26 year old single girl, suddenly realized that her genitals were wet. Investigation revealed copious vaginal bleeding which did not resemble her menses. This incident and three subsequent ones occurred between menstrual periods which were regular and normal. Several competent gynecologic examinations failed to disclose any cause for the bleeding. During the same months when these episodes were occurring Mary experienced a variety of lesions about the mouth. For many years she had neglected the care of her teeth. During the time under discussion, moreover, she developed repeated canker sores about the mouth, a stone in Stenson's duct and several episodes of unexplained pain in the jaws. Finally a chance x-ray revealed a large cyst of the mandible. The outstanding aspect of the psychiatric picture was a severe phobia. Mary was subject to attacks of fright while being interviewed, while eating opposite someone in a public place, while riding in trains etc. She was especially panicky in the dentist's chair, particularly when the x-ray tube was pointed at her mouth. She had a profound aversion to all manner of birds and to red meat. The onset of her acute illness began rather abruptly while she was a student in college. Up to the time of the following incident she had been quite happy in her studies. She had participated in discussions and she liked to sit in the front row at lectures, often staring and smiling at the instructor,

especially if he were attractive. One day under such a circumstance all her papers fell to the floor. The lecturer, a good looking man, stopped talking, stepped off the platform, knelt down, picked up the papers and returned them to her. At first she thought little about the incidence but shortly thereafter it began to prey on her mind. Within a short time she began to develop the anxiety attacks already mentioned.

For the first nine years of her life Mary had been the only child in a quarrelsome and unhappy household. Her mother, an unstable "hysterical" woman used threats and bribes to get Mary to eat. Moreover, she made frequent suicidal threats. At the age of eight years Mary learned that a pregnant neighbor had to undergo some type of operation because of bleeding. It was said that something was taken out of this woman and placed in a glass. Thereafter Mary refused to drink out of a glass. At about the same time she was frightened by seeing a chicken killed. From that time on her dietary habits changed. She refused to eat meat, fish or fowl. Eggs disgusted her and she was repelled by all red foods including radishes and tomatoes. At about this time she began to develop a fear of birds. She even came to loathe the sight of feathers on a hat, declaring they made her want to vomit. When Mary was nine years of age her mother gave birth to a boy, an event which allegedly came as a complete surprise to Mary. Her first recollection of this boy was his circumcision. Her parents seemed to dote on him and Mary felt quite isolated. As she grew older she manifested considerable intellectual ambition, and as a secretary later on in a law office was often accused by her employer of overstepping her role. Her relationships with men were usually troublesome, quarrelsome and unhappy, ending, as a rule, with her feeling ill treated and rejected. When she finally married it was to a man younger than herself who was unable to support her. During her treatment she was unable to discuss any significant aspect of her sexual activities. She declared she had never seen her husband's penis and that the thought of seeing it frightened her. She averred that she desired to get men interested in her so that she might first control them and then discard them. In this role she fancied herself a modern Circe who turned men into pigs. She showed a similar interest in defeating the therapist, and entertained phantasies of throwing his medical books out of the window.

It was evident that Mary's extremely insecure childhood had promoted the feeling of being mutilated and deprived. As a consequence, she developed strong aggressive biting impulses which she defended herself against by means of a vegetarian diet. At the same time she avoided eating anything red which might remind her of her cannibalistic impulses. With the birth of a favored brother there developed a reinforcement of these aggressive and hostile attitudes which later were extended to other men with whom she endeavored to compete and whom she tried to degrade. The acute outbreak of her phobic symptoms occurred when her instructor stopped his lecture to pick up her papers, an event which to her represented his being castrated through being humbled. The rapid evolution thereafter of her phobic state indicated that her previous defenses against her desires to castrate men were no longer adequate.

The first episode of vaginal bleeding occurred while she was cleaning a chicken, an object which in her childhood and adolescence had been a source of fright and disgust. The major basis of her bird phobia lay in its classic phallic symbolism. Thus cleaning a chicken signified cutting and plucking a penis symbol, and as such a realization of her biting and mutilating phantasies. Her own bleeding at that moment may therefore be interpreted as a self-castration: what she does to the penis she must do to herself as well. Three subsequent episodes of bleeding occurred under circumstances which may again be regarded as having active castrating significance to her. The second took place while she was reading psychoanalytic literature, a practice about which she was secretive and guilty, feeling that it represented an effort to compete with and destroy the analyst. The third episode took place under the following circumstances: she was requested to appear in court to testify in a case with which she had been familiar when working in a law office. Her phobia made such an appearance impossible. Accordingly she was permitted to give testimony in her own home to a clerk sent there by the court. While awaiting his arrival, during which time she felt quite consciously elated because "They are obliged to come to me," she began to bleed. The last episode took place a day or two after she learned that her brother, one of the earliest objects of her castrating impulses was "on the verge of TB."

Thus in this case active castrating impulses were dealt with in several ways. 1) She developed a fear of the object of her sadistic drives. 2) She avoided eating those foods which stood as symbols of human flesh. 3) Through the development of mouth lesions and neglect of her teeth she made herself less capable of carrying out orally destructive urges. 4) Through bleeding vaginally she managed to make herself instead of the male genital the victim of her castrating impulses.

In this presentation there have been described in brief some of the somatic implications of what is termed the castration complex in women. In the space allotted to such a discussion one can do no more than hint at the complexities and ramifications of this most interesting aspect of human psychology, a meeting place in truth for medicine, religion, sociology, mythology, poetry, and the fairy tale.

Jason: O my children, how vile a mother ye have found.

Medea: My sons, your father's feeble lust has been your ruin.

Jason: 'Twas not my hand at any rate that slew them.

Medea: No, but thy foul treatment of me, and thy new marriage.

Jason: Didst think that marriage enough to murder them?

Medea: Dost think a woman counts this a trifling injury?

BIBLIOGRAPHY

1. FREUD, S.: Three Contributions to the Theory of Sex, in *The Basic Writings of Sigmund Freud*. Modern Library, New York, 1938.
2. ABRAHAM, K.: Manifestations of the Female Castration Complex, in *Selected Papers*. p. 338, Hogarth Press, London, 1942.
3. LEWIN, B.: The Body as Phallus. *The Psychoanal. Quart.*, 2: 24, 1933.
4. DE MILLE, AGNES: *Dance to the Piper*. Little, Brown and Co., Boston, 1952.
5. SILBERMANN, I: A Contribution to the Psychology of Menstruation. *Internat. J. of Psychoanal.*, 21: 258, 1950.

6. PELLER, S.: Wiener Med. Wochenschrift, 85: 1935.
7. BRUSH, A. L.: Attitudes, Emotions and Physical Symptoms Commonly Associated with Menstruation in 100 Women. Amer. J. of Orthopsych., 8: 286, 1938.
8. CHADWICK, M.: The Psychological Effects of Menstruation. Nervous and Mental Disease Monograph Series, No. 56, 1932.
9. DEVEREUX, G.: The Psychology of Feminine Genital Bleeding. Internat. J. Psychoanal., 21: 237, 1950.
10. GILL, M. M.: Functional Disturbances of Menstruation. Bull. Menninger Clin., 7: 6, 1943.
11. REIDER, N.: Menarche After One Psychotherapeutic Interview. Bull. Menninger Clin., 7: 45, 1943.
12. MENNINGER, K.: Psychogenic Influences on the Appearance of the Menstrual Period. Internat. J. of Psychoanal., 22: 60, 1941.
13. BALINT, M.: A Contribution to the Psychology of Menstruation. Psychoanal. Quart., 6: 346, 1937.
14. MILLER, J. A.: Psychogenic Menorrhagia. Med. J. and Rec., 134: 84, 1931.

FAILURE OF REPEATED INTRAPERITONEAL INJECTION OF HYALURONIDASE TO PREVENT RECURRENCE OF ABDOMINAL ADHESIONS IN RATS*

ROBERT J. WILDER, M.D.

Recently, interest has arisen concerning the use of hyaluronidase for the prevention of peritoneal adhesions. Chandy and Rhoads (1) have used talcum powder intraperitoneally in rats to produce adhesions and simultaneously instilled hyaluronidase into the peritoneal cavities of their test animals. All of their animals developed adhesions with talc alone. They found 60 per cent of 20 animals to have no lesions when hyaluronidase was used. Following this, Thomas (2) produced adhesions by clamping the cecum of rats, thus injuring the serosal surface. Seventy-six per cent of 55 rats treated with simultaneous instillation of hyaluronidase formed adhesions while 89 per cent of 55 animals who were not treated formed adhesions. Connolly and Richards (3) produced adhesions in 14 dogs with talcum powder and then at a second operation lysed the adhesions and instilled hyaluronidase locally in 7 dogs before closing the abdomen. They reported no recurrences of adhesions in 5 of 7 dogs and a few recurrent adhesions in the two remaining dogs who had received smaller amounts of hyaluronidase. All seven controls developed recurrent adhesions.

In all of the above work hyaluronidase was administered only once; at the time of the initial procedure. Yet blood, hyaluronic acid and raw surfaces may remain in the abdomen for days while hyaluronidase itself diffuses away and is destroyed in a matter of hours. Therefore, it was deemed worthwhile to investigate the prolonged use of hyaluronidase in the prevention of recurrent abdominal adhesions.

This experiment consists of lysing abdominal adhesions in rats and attempting to prevent the formation of recurrent adhesions by the use of large intraperitoneal doses of hyaluronidase† over a long period of time.

PROCEDURE

Forty-three Long Evans rats were used. A solution of 30 per cent talc in saline was injected intraperitoneally through a number 20 needle. At the end of a month, under ether and subcutaneous nembutal anesthesia, a long mid-line incision was made and the abdominal cavity inspected. All adhesions were lysed by blunt and sharp dissection after which 5 cc. of saline were instilled into the peritoneal cavity of the control rats and 5 cc. of saline with 500 units of hyaluronidase in the test animals. Closure of the abdomen was performed in two layers with silk. The control animals received 3 cc. of saline injected intraperitoneally once daily for seven days thereafter while the test animals received 500 units of hyaluronidase in 3 cc. of saline injected intraperitoneally every day for seven days. The rats were allowed to live for another month and were then

* From the Department of Surgery of The Mount Sinai Hospital, New York.

† The hyaluronidase used in these experiments was supplied by the Wyeth Incorporated, 1401 Walnut Street, Philadelphia 2, Pa.

sacrificed and explored for recurrent intraperitoneal adhesions. Of the 43 rats used in this series, 5 did not form adhesions, 4 died of intestinal obstruction before lysis was attempted, and 3 died from the surgical procedure, thus leaving 31 animals.

Analysis of adhesions was carried out by recording the number of actual adhesions seen and lysed, and also the number of centimeters of bowel that adhered to itself. A description was recorded in each case with a clinical impression of the situation.

RESULTS

On exploration of the abdominal cavity one month after the injection of a 30 per cent solution of talc, numerous talc granulomas were seen as well as matted loops of bowel and numerous adhesions involving ovarian tissue, spleen, liver and omentum. All the adhesions were lysed with fine scissors and the matted bowel freed. Although much bowel was partially compromised by this procedure, most of the animals recovered. Of the 31 rats that survived the entire procedure, 15 were controls and 16 received hyaluronidase at the time of lysis and for seven days thereafter. Of the 15 controls, 7 reformed adhesions practically identical with those which had been lysed one month earlier, 6 showed a slight decrease in adhesions, and 2 had a greater number of adhesions than had been previously divided. In the 16 test animals, 9 had identical adhesions, 3 had fewer adhesions and 3 had more adhesions than those originally lysed. There was, thus, no appreciable difference in the reformation of adhesions in control and test animals. Under the conditions of the experiment, hyaluronidase had no effect on the reformation of mechanically lysed adhesions that were initially produced by talcum powder.

SUMMARY

1. In 31 rats, intraperitoneal adhesions were produced by the instillation of talcum powder.

2. Adhesions were surgically lysed. Sixteen animals were treated for seven days with intraperitoneal hyaluronidase injections of 500 units per day, and 15 were treated with saline injections.

3. There was no difference in the reformation of adhesions in the rats treated with hyaluronidase and in those treated with saline.

REFERENCES

1. CHANDY, J. AND RHOADS, J. E.: Experimental Studies on the Mechanism of the Formation of Intraperitoneal Adhesions. *Fed. Proc.*, 5: 218, 1946.
2. THOMAS, J., JACKSON, G., PORTNOFF, C., CHANDY, J., AND RHOADS, J. E.: Further Experiments on Influence of Hyaluronidase on the Formation of Intraperitoneal Adhesions in the Rat. *Proc. Soc. Exp. Biol. & Med.*, 74: 497, 1950.
3. CONNOLLY, J. E. AND RICHARDS, V.: Experimental Use of Hyaluronidase in the Prevention of Adhesions. *Surgical Forum of the Clinical Congress of the American College of Surgeons*, 85, 1951.

THE MEDICAL TEACHING MISSION TO ISRAEL AND IRAN

LEO M. DAVIDOFF, M.D.

A medical teaching mission was active in Israel during the month of September, 1951, and Iran during October, 1951. It consisted of an international group of medical scientists. The Chairman was Dr. Leo Davidoff and the Vice Chairman, Dr. Karl Evang. The World Health Organization was represented by Dr. Edward Grzegorzewski and the Unitarian Service Committee by Mr. Howard L. Brooks who was also the Administrative Director of the Mission. Two secretaries accompanied the mission, one from the World Health Organization, Miss Monica Legh-Jones and one from the Unitarian Service Committee, Mrs. Enid Tennyson Davis.

The personnel included Dr. Gordon Kenneth Moe who is Professor of Physiology at the State University of New York. In Biochemistry we had Dr. Hugo Theorell, Professor of Biochemistry and Head of the Biochemical Department of the Medical Nobel Institute of Stockholm, Sweden. Dr. Paul Klemperer, Pathologist to Mount Sinai Hospital and Professor of Pathology at Columbia University College of Physicians and Surgeons of New York, represented his field. Internal Medicine was covered by Dr. Erik Warburg, Professor of Medicine at the University of Copenhagen, Denmark; and Pediatrics by Dr. Samuel Z. Levine, Professor of Pediatrics, Cornell University Medical College, New York. Lectures and demonstrations in General and Thoracic Surgery were given by Dr. Carl Semb, Professor of Surgery at the University of Oslo, Norway; and those in Neurosurgery by Dr. Leo M. Davidoff, Neurosurgeon to Mount Sinai and Beth Israel Hospitals in New York and Clinical Professor of Neurosurgery, New York University. The Orthopaedic Surgeon was an Englishman, Mr. H. Osmond-Clarke, Honorary Surgeon and Assistant Director, The Orthopaedic and Accident Hospital, London. The Radiologist was Dr. Leo G. Rigler, Professor of Radiology, University of Minnesota, School of Medicine, Minneapolis, Minnesota. Anaesthesiology was covered by Dr. Lucien E. Morris, Associate Professor of Anaesthesiology, State University of Iowa, College of Medicine, Iowa City, Iowa. The Advisor on Medical Education was Dr. E. Gryzegorzewski, Professor of Public Health, Former Rector of the Medical Academy of Gdansk, at present Director of Division of Education and Training Service, World Health Organization, Geneva, Switzerland. The Public Health team was headed up by Dr. Karl Evang, Director General of Public Health, Oslo, Norway. Epidemiology was under the direction of Dr. John E. Gordon, Professor of Preventive Medicine and Epidemiology, Harvard University School of Public Health, Boston, Massachusetts. Environmental Sanitation was the special concern of Dr. Richard G. Tyler, Professor of Environmental Sanitation at the University of Washington, Seattle, Washington.

The mission was sponsored jointly by the World Health Organization and the Unitarian Service Committee. The World Health Organization by its participation in this project was fulfilling one of its functions: to promote *health*

on a global scale. In the preamble to its constitution, it defines "health" as "a state of complete physical, mental and social well being and not merely the absence of disease or infirmity."

The wisdom of the founders of the World Health Organization is further illustrated by the remainder of the preamble to the constitution, which declares, among other things, that "the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being, without distinction of race, religion, political belief, economic or social condition," and that "unequal development in different countries in the promotion of health and control of disease, especially communicable disease, is a common danger."

Among the many ways to achieve its objectives, the World Health Organization has provided means to "assist governments upon request in strengthening health services; to promote cooperation among scientific and professional groups which contribute to the advancement of health; to promote improved standards of teaching and training in the health, medical and related professions."

The co-sponsor of this mission, the Unitarian Service Committee, was founded in May, 1940 as a standing committee responsible to the Board of Directors of the American Unitarian Association, which instructed the Committee to engage in humanitarian service at home and abroad without discrimination as to race, color, nationality or religious convictions.

It is apparent how these two organizations with closely similar aims would become natural partners in the promotion of such missions as the one with which we are here concerned. This partnership moreover is intimate and includes joint responsibility for both the planning and execution of these projects.

But these missions began even before the formation of the World Health Organization. At the end of the war in 1945, starvation, malaria and other infectious diseases were devastating thousands of children in Italy. The Unitarian Service Committee sent a team of medical experts in public health and pediatrics to report upon the situation to suggest remedies for its alleviation. This mission was so successfully accomplished that it gave direction to the work of the Committee ever since. In 1946 the first two of a series of missions with help from UNRRA were sent, one to Czechoslovakia and one to Poland. When UNRRA ceased functioning, the WHO stepped in and in addition to financial support, acted as a co-sponsor to numerous subsequent missions. Dr. Erwin Kohn, on being mustered out of the United States Medical Corps, was employed by the Committee and soon was placed in charge of organizing these missions. The writer had the pleasure of being a member of the mission to Czechoslovakia in 1946, and the honor of being chairman of the mission to Poland and Finland in 1948.

Some years as many as five missions to five different countries or more were organized.

Usually a request for a mission is sent out by a country directly to WHO or indirectly through the Unitarian Service Committee. If the need for a mission by that country is recognized, the wheels start turning and at the end of

about six months, the mission is finally on its way. The interval is filled with active preparation by the country to be visited, by the Unitarian Service Committee in Boston and New York, and by the WHO in Geneva.

The specialties to be represented by mission members are determined by a preliminary committee of the Health Ministry and various other medical agencies of the country. This being decided, the mission personnel must be selected and screened for their eminence in their field, their wisdom, personal attributes and sympathy with the medical problems of the country to be visited. Each member must be acceptable unanimously by all parties involved.

The host country must then list its most urgent needs in materials, books, instruments and other supplies. The Unitarian Service Committee must, on the other hand, make the available funds stretch to supply these requirements by asking contributions from publishers, drug manufacturers, instrument makers and private individuals.

Meanwhile the host country has had a carefully selected preparatory committee at work to decide on what program for the mission will result in the greatest benefit for its medical profession.

Finally a representative of the World Health Organization visits the country for several weeks preliminary to the arrival of the mission and together with the preparatory committee thrashes out every last detail of both medical and practical nature. By the time the mission arrives, considerable interest among physicians and the general public has been aroused.

When the members of the mission arrive, they may find their curriculum completely worked out with a printed brochure giving in detail the program for the mission as a whole and for each particular member. The work of the mission consists not only of a series of lectures by the various members to the general medical public, but the major work of the mission is for each member to associate himself with his counterpart in his own specialty in the country visited, most of the work being done in each department on the basis of daily interchange of information, ward rounds, demonstration of techniques, operations, staff meetings, conferences, symposia, etc.

In addition to the work in individual departments, the members of the mission as a whole are drawn into joint activities, such as clinico-pathological conferences, clinical conferences and round table discussions on selected subjects.

Books and instruments are presented, as well as drugs and other medical and surgical supplies.

While the work of the mission is tremendously helpful to the country visited at the time when the mission is active, probably the most important results of such missions are the follow up achievements after the mission is gone. These consist of the passage of health legislation which the local authorities can press through their legislative bodies with the authority of the mission members behind them; the establishment of teams for the treatment of tuberculosis; the elimination of malaria; the organization or the reorganization of medical school departments and hospital services; the arrangement for, and the selec-

tion of young physicians from the country to travel abroad, but especially to the countries of origin of the members of the mission to acquire further medical training and experience

Not the least results of such missions is the opportunity for international friendship and understanding, both among the personnel of the mission originating from different countries and between them and the medical profession, as well as the general public of the country visited.

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CONTENTS

PROBLEMS IN THE TREATMENT OF REFRACTORY BACTERIAL INFECTIONS. <i>Morton S. Bryer, M.D. and S. Stanley Schneierson, M.D.</i>	285
PSYCHODYNAMIC DISTURBANCES IN PATIENTS WITH TEMPORAL LOBE DISORDER. <i>Mortimer Ostow, M.D.</i>	293
AN INTRODUCTION TO THE PATHOGENESIS OF VIRAL INFECTIONS. <i>Alfred L. Florman, M.D.</i>	309
LOCALIZED HYPERTROPHIED GASTRIC FOLDS: DIFFERENTIATION FROM CARCINOMA OF THE STOMACH. <i>Stuart I. Gurman, M.D. and Bernard S. Wolf, M.D.</i>	315
ABSENCE OF RIGHT KIDNEY: RETROPERITONEAL CYST. <i>Gordon D. Oppenheimer, M.D., and Joseph M. Silagy, M.D.</i>	324

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* Deceased

PROBLEMS IN THE TREATMENT OF REFRACTORY
BACTERIAL INFECTIONS*

MORTON S. BRYER, M.D. AND S. STANLEY SCHNEIERSON, M.D.

New York, New York

The availability of the modern antibiotics has brought many changes to the treatment and prognosis of infectious disease. However, none is more striking than the fall of the virulent organisms, such as the pneumococcus and Beta hemolytic streptococcus, to positions of minor therapeutic importance and the rise of the lesser pathogens and organisms previously considered as saprophytes to the respect they presently command. It is fortunately true that the most virulent organisms are markedly suppressed or destroyed by our present antibiotics and that resistance is uncommon or non-existent. This happy situation may well stem from the more exacting, and thus readily blocked, metabolic requirements of organisms whose entire life cycle depends upon the complex products of the animal body economy. The less virulent organisms such as *B. proteus*, *Pseudomonas aeruginosa*, the coli-aerogenes group, the *Staphylococcus aureus* and the enterococcus have less rigid metabolic requirements. It is such organisms that are found, with increasing frequency, to be resistant to the antibiotics in common use.

These five groups of bacteria cause infections that are frequently refractory to ordinary therapy with our least toxic antibiotics. However, it is best to exhaust all therapeutic possibilities before resorting to chemicals of a more toxic nature. We will consider these organisms separately with this principle as a guide.

REFRACTORY ORGANISMS

B. proteus is frequently the cause of highly resistant urinary and occasional systemic infections. On a weight basis, this organism is most actively inhibited or killed by neomycin (1-4). However, it is well to remember that often streptomycin (to be used in antibiotic combinations only) chloromycetin (chloramphenicol), sulfonamides, or furadantin may be effective singly or in combinations. When the *B. proteus* infection is resistant to the latter chemotherapeutic agents neomycin may become the drug of choice. It can be administered intramuscularly if the auditory and nephrotoxic actions (5) are carefully evaluated. We have found neomycin to be life saving in bacterial endocarditis, septicemias and abscesses as well as urinary tract infections. Resistance of a marked degree has been rare and the bactericidal property of neomycin (1) makes it particularly valuable in endocarditis where this effect is most essential (51).

Pseudomonas Aeruginosa has been found more frequently as a cause of urinary tract infection, septicemia, bacterial endocarditis, meningitis, and skin or burn

* From the Departments of Medicine and Microbiology, The Mount Sinai Hospital, New York, N. Y.

infections since the introduction of antibiotic therapy. Polymyxin (aerosporin) has been shown to have the greatest activity against this organism with neomycin a close second (2, 3). However, again it must be noted that many of these infections may respond to less toxic chemotherapeutic agents such as streptomycin (to be used in combination only), terramycin (oxytetracycline), chloromycetin (chloramphenicol), furadantin or sulfonamides singly or in combination. When the causative bacteria are resistant to the above agents, however, polymyxin (aerosporin) can be administered intramuscularly if precautions are carefully observed and the drug discontinued at the first indication of oliguria. We have treated many serious infections without difficulty and with dramatic results (6, 7). Resistance to polymyxin (aerosporin) is rarely found and like neomycin its effect upon microorganisms is bactericidal (8).

The Coli-Aerogenes group of bacteria has demonstrated a gradually increasing resistance (9) to most antibiotics over a period of years although the majority of organisms still remain within the therapeutic range of aureomycin (chlortetracycline), terramycin (oxytetracycline), chloromycetin (chloramphenicol), streptomycin (in combination) or the sulfonamides. Infections caused by this group will usually respond to one or a combination of the above antibiotics to which they are most sensitive. However, if the strain of organism is completely resistant to the previously considered antibiotics it may still be sensitive to polymyxin or neomycin.

The Staphylococcus aureus has developed a steadily increasing resistance to penicillin since that antibiotic was first introduced (10, 11, 12, 16). As shown in several studies in England and the United States over 80% of these strains were sensitive to penicillin prior to 1946, but since then the percentage of sensitive organisms have fallen to less than 50% of the strains now isolated in hospitals. It is interesting that most highly resistant organisms of this species, cultured from patients are penicillinase producers (22, 23, 25) and that a higher percentage of resistant strains are isolated from hospital populations than from the community at large (11-15). These observations fit well with the origin of resistance as a result of the selective action of antibiotics on the varied bacterial populations (22, 24) and resulting cross infections (18, 19, 20). This loss of susceptibility of staphylococci has also been noted for aureomycin (chlortetracycline) (9) and terramycin (oxytetracycline) (17, 18). When dealing with sensitive organisms penicillin is the most active antibiotic but resistant organisms may respond to chloromycetin (chloramphenicol), aureomycin (chlortetracycline), terramycin (oxytetracycline), or the sulfonamides. However, the antibiotics of choice in penicillin resistant staphylococcal infections are erythromycin (ilotycin or erythrocin) (26, 27, 28) and magnamycin (carbomycin) (31). There is some clinical (21, 29) and laboratory evidence (26-29) that resistance will appear to these newer antibiotics as they are more widely prescribed. However, at present, the great majority of strains are sensitive to erythromycin (ilotycin or erythrocin) and magnamycin (carbomycin). In addition, the action of the latter drugs is bactericidal (30) for some strains of staphylococci. This may prove of great importance in the treatment of staphylococcal endocarditis. Although bacitracin

and neomycin are also active against staphylococci the less toxic erythromycin (ilotycin or erythrocin) or magnamycin (carbomycin) have restricted their role to possible use in endocarditis, where their bactericidal activity might be of advantage. The nephrotoxic action of bacitracin is similar to that of polymyxin (32, 33).

Enterococci have been a persistent problem in therapy of bacterial endocarditis, urinary tract infections and sepsis. These organisms tend to be relatively resistant to penicillin and have demonstrated increasing resistance to aureomycin (chlortetracycline) (9). The special requirement of bactericidal activity for successful treatment of enterococci endocarditis limits the therapy of this condition to combinations of streptomycin, penicillin and bacitracin. However, where erythromycin or magnamycin demonstrate bactericidal in vitro activity, for the strain isolated, a trial of therapy would be justified. The broad-spectrum bacteriostatic antibiotics, such as aureomycin, terramycin, chloromycetin, and the sulfonamides, are usually effective in urinary tract infections caused by the enterococci, but erythromycin or magnamycin may well become the drugs of preference.

Thus it has been noted that following the general use of the antibiotics an increasing percentage of strains of *B. proteus*, *Pseudomonas aeruginosa*, *coli-aerogenes*, the *Staphylococcus aureus*, and the enterococcus have emerged as resistant organisms. Of critical importance in the treatment of refractory infections, therefore, is the availability of a laboratory capable of determining which of the therapeutic agents is most apt to prove effective (34). The comparative study requires standardized laboratory procedures with use of the tube dilution technique. The agar plate diffusion methods of estimating activity are useful for gross relative values but do not permit quantitative comparison of different antibiotic activities nor demonstrate bactericidal effect.

DRUGS USEFUL IN REFRACTORY INFECTIONS

The Polymyxins (aerosporins) are basic polypeptide antibiotics derived from cultures of the soil bacillus, *B. polymyxa* (35, 36, 37). There are at least five similar chemical compounds that have been isolated from this group of antibiotics. These differ in their amino acid composition and have been labeled alphabetically A, B, C, D and E, however, all contain L- α , γ diamino butyric acid and a C₉ fatty acid (38). Dextro rotatory isomers of amino acids are present in polymyxin A, B and D and since they are not usually found in the body it is thought by some that these compounds may account for some of the renal toxicity noted with higher doses. However, in our experience, this damage to renal tubules is not prevented by administration of dl-methionine as has been suggested (39, 52).

The activity of the polymyxins is strongly bactericidal and sharply limited to gram negative bacilli (8). With the exception of *B. proteus*, these compounds are active against such bacilli in minute quantities. By utilizing total daily doses of 2 to 5 mg. per kg., and observing the patient carefully, marked therapeutic activity can be obtained with only minor toxic reactions (6, 7). The ad-

ministration of intramuscular polymyxin is frequently accompanied by a drop in the specific gravity of the urine, albuminuria and casts. However, these findings do not necessitate cessation of therapy. All patients receiving these antibiotics must have their daily urinary output carefully recorded and a marked drop in volume (below 500 cc. per twenty four hours for adults) is indication for suspending treatment. Oliguria is a danger sign of impending anuria. Fever and paresthesias occur as minor toxic reactions that are annoying but not dangerous. These side effects, as well as renal tubular damage are reversible when treatment is stopped. However, these antibiotics must be administered with the greatest caution to patients with renal insufficiency (40) since they are most likely to develop anuria.

Polymyxin B is commercially available as 50 mg. (500,000 units) of dried crystalline powder in a sterile vial. Since toxicity depends upon the rapidity of administration (33), it is important to give this antibiotic in four to six daily intramuscular injections so that individual doses do not exceed 1 mg. per kg. Such injections are painful and best diluted in 1 or 2 per cent procaine. Polymyxin does not penetrate readily from the blood to the spinal fluid (33). When administered into the spinal fluid in meningitis caused by sensitive organisms, polymyxin should be injected slowly, well diluted in spinal fluid, and the total dosage should be kept to 1 mg. or less for adults (60 kg.) and reduced accordingly for smaller individuals. Doses of 5 or 10 mg. intrathecally in dogs may cause neurological changes while a dose of 1 mg. is without this toxic effect (33, 43). Polymyxin, like neomycin, and bacitracin is poorly absorbed from the gastrointestinal tract when administered orally and may be employed for local action on intestinal organisms (41, 42).

Neomycin is a stable, basic crystalline antibiotic obtained from the *Streptomyces fradiae* (1-5). It has marked bactericidal activity against most gram negative organisms, in low concentrations, and is effective in higher concentrations against many gram positive bacteria as well. It is effective against the tubercle bacillus and resembles streptomycin in its antimicrobial spectrum. However, resistant organisms have not appeared as readily with neomycin (1, 44). The side effects of this antibiotic resemble those of dihydrostreptomycin rather than streptomycin in first producing damage to the auditory portion of the eighth nerve before disturbing vestibular function. In addition, neomycin is capable of producing a nephrotoxic action similar but less marked than that of polymyxin and bacitracin (5).

At least two chemically and biologically different types of neomycin have been identified. They are designated as neomycin A and B (45) and are basic compounds, most active in alkaline medium, thermostable and soluble in water.

Despite the renal and auditory complications, neomycin can be administered intramuscularly if similar precautions as noted for polymyxin are taken. Oliguria or a detrimental change in audiometrics indicates prompt cessation of therapy. If renal insufficiency is already present even greater caution is necessary since blood levels may be higher through faulty excretion and, therefore, damage is more likely to occur. In our experience, no difficulty has been encountered, even

in urinary tract infections, when a total daily dose of 10 mg. per kg. or approximately 2,000 units per kg. is divided into four equal intramuscular injections and administered at six hour intervals. A combination of neomycin and bacitracin has been used simultaneously in the same patient without ill effect. The maintenance of a daily urinary output in excess of 500 cc. is most important. Since neomycin, polymyxin, and bacitracin are irritating locally, it is well to make up the solution to be injected in 1 or 2 per cent procaine.

Bacitracin is a basic polypeptide antibiotic derived from a strain of the *Bacillus subtilis* (47). It is markedly bactericidal for most of the gram positive organisms and combined with penicillin or streptomycin may be effective in the treatment of resistant bacterial endocarditis. As noted with polymyxin, bacitracin does not readily penetrate the cerebrospinal fluid barrier and, in adults, doses of 10,000 units may be injected intrathecally where necessary in the treatment of meningitis (46). It is also similar to the former antibiotic in its potential for causing renal tubular damage when administered in large doses (32).

When dissolved in procaine and injected intramuscularly in a daily dose of 1,000 units per kg., serious toxic reactions are uncommon. The total daily dose is best administered in four injections at six hour intervals. The record of daily urine output and the BUN or NPN will serve as indications of toxicity. As with neomycin and polymyxin, when urine output falls below 500 cc. per day or BUN or NPN rise sharply, therapy must be discontinued. With all three drugs, some albuminuria, casts, and a drop in specific gravity of urine is to be expected. In a patient with evidence of renal damage, great care must be exercised.

Erythromycin (ilotycin or erythrocin) and *Magnamycin* (carbomycin) are two new antibiotics that are very effective against most of the gram positive organisms, rickettsiae and larger viruses when administered orally. They are crystalline, basic compounds whose antibacterial spectrum closely parallels that of penicillin (26-31). The former is produced by the *Streptomyces erythreus* and the latter by the *Streptomyces halstedii*. However, their similar pattern of activity and the fact that an organism made resistant to one will show cross resistance (48) to the other, makes it highly probable that they are of similar chemical structure, or analogs, as is true of aureomycin and terramycin (49). In general, slightly more magnamycin is required, on a weight basis, to inhibit a sensitive organism (48).

These two similar antibiotics are of low toxicity. Their side effects consist of occasional diarrhea, nausea, vomiting, and skin reactions as seen with aureomycin, terramycin, and chloromycetin. It is interesting that they demonstrate a bactericidal as well as bacteriostatic (30) action for certain organisms. This activity may be utilized in the treatment of bacterial endocarditis. However, their greatest asset is that staphylococci and enterococci, even though resistant to aureomycin, terramycin, chloromycetin, penicillin, streptomycin and the sulfonamides are usually sensitive to erythromycin and magnamycin (26-31). In total oral daily doses of 20 to 40 mg. per kg., administered at four to six hour intervals, both antibiotics appear effective and are well tolerated.

Furadantin, N-(5-nitro-2 furfurylidene)-1-aminohydantoin, is a stable, yellow

crystalline compound which offers such desirable characteristics as a broad antibacterial spectrum, including both grams negative and positive organisms, and so far little tendency for bacteria to develop resistance. It is not active against viruses, rickettsiae, or fungi although some effect on protozoa has been described (50).

Nausea and vomiting in a considerable number of patients seem to be the only toxic effects noted to date. Furadantin is excreted in the urine in high concentration. This property and its activity against *B. proteus*, *pseudomonas aeruginosa*, and *aerobacter aerogenes* make it worthy of trial in refractory urinary infections involving these organisms.

SUMMARY

1. *B. proteus*, *Pseudomonas aeruginosa*, *Coli-aerogenes* organisms, *Staphylococcus aureus*, and the enterococci are notable as the etiological agents of bacterial infections which are refractory to the antibiotics in common use.

2. Polymyxin, neomycin, and bacitracin are more toxic antibiotics that may be employed provided precautions are observed.

3. Erythromycin, magnamycin, and furadantin are more recent antibiotic and chemotherapeutic agents which may be of some assistance in combating organisms resistant to the older drugs.

4. The key to successful therapy of refractory infections is found in rigidly standardized and controlled laboratory sensitivity determinations.

BIBLIOGRAPHY

1. WAKSMAN, S. A., AND LECHEVALIER, H. A.: Neomycin, a new antibiotic active against streptomycin-resistant bacteria, including tuberculosis organisms. *Science*, 109: 305, 1949.
2. WARTH, P. Y., CHANDLER, C. A., AND BLISS, E. A.: The antibacterial action of neomycin furadroxyl in vitro and in vivo. *Bull. Johns Hopkins Hosp.*, 86: 169, 1950.
3. WAISBREN, B. A., AND SPINK, W. W.: Comparative activity of Q-19, neomycin, aureomycin, polymyxin B and chloromycetin against gram negative bacilli. *Proc. Soc. Exper. Biol. and Med.*, 74: 35, 1950.
4. FELSENFELD, O., VOLINI, I. F., ISHIHARA, S. J., BACHMAN, M. C., AND YOUNG, V. M.: A study of the effect of neomycin and other antibiotics on bacteria, viruses, and protozoa. *J. Lab. and Clin. Med.*, 35: 428, 1950.
5. WAISBREN, B. A., AND SPINK, W. W.: A clinical appraisal of neomycin. *Ann. Int. Med.*, 33: 1099, 1950.
6. SCHOENBACH, E. B., BRYER, M. S., BLISS, E. A., AND LONG, P. H.: Polymyxin: A note on experimental and clinical investigations. *J. A. M. A.*, 136: 1096, 1948.
7. SCHOENBACH, E. B., BRYER, M. S., AND LONG, P. H.: The clinical use of polymyxin. *Ann. N. Y. Acad. Sci.*, 51: 987, 1949.
8. BLISS, E. A., CHANDLER, C. A., AND SCHOENBACH, E. B.: In vitro studies of polymyxin. *Ibid.*, 51: 944, 1949.
9. SCHNEIERSON, S. S.: Changes in bacterial sensitivity to aureomycin and chloramphenicol in the course of the past three years. *J. Lab. and Clin. Med.*, 40: 48, 1952.
10. RAMMELKAMP, C. H., AND MAXON, T.: Resistance of staphylococcus aureus to the action of penicillin. *Proc. Soc. Exper. Biol. and Med.*, 51: 386, 1942.
11. BARBER, M., AND ROZEVADOWSKA-DOWZENKO, M.: Infection by penicillin-resistant staphylococci. *Lancet*, 2: 641, 1948.

12. BARBER, M., AND WHITEHEAD, J. E. M.: Bacteriophage types in penicillin-resistant staphylococcal infection. *Brit. M. J.*, 2: 565, 1949.
13. FORBES, G. B.: Infection with penicillin-resistant staphylococci in hospital and general practice. *Ibid.*, 2: 569, 1949.
14. BOE, J., AND VOGELSAJG, T. M.: Penicillin-resistant pathogenic staphylococci. II. Increasing incidence of resistant strains in the upper respiratory tract. *Acta Pathologica et Microbiologica Scandinavica*, 29: 368, 1951.
15. VOGELSAJG, T. M.: The incidence of penicillin-resistant pathogenic staphylococci isolated from the upper respiratory tract of young, healthy persons. *Ibid.*, 29: 363, 1951.
16. WELCH, H.: Editorial: The antibiotic-resistant staphylococci. *Antibiotics and Chemotherapy*, 3: 561, 1953.
17. FINLAND, M., AND HAIGHT, T. H.: Antibiotic-resistance of pathogenic staphylococci. *Arch. Int. Med.*, 91: 143, 1953.
18. CLARKE, S. K. R., DALGLEISH, P. G., AND GILLESPIE, W. A.: Hospital cross-infections with staphylococci resistant to several antibiotics. *Lancet*, 1: 1132, 1952.
19. BARBER, M., HAYBOE, F. G. V., AND WHITEHEAD, J. E. M.: Penicillin-resistant staphylococcal infection in a maternity hospital. *Ibid.*, 2: 1120, 1949.
20. ROWNTREE, P. M., AND THOMSON, E. F.: Incidence of antibiotic-resistant staphylococci in a hospital. *Ibid.*, 2: 262, 1952.
21. DEARING, W. H., AND HEILMAN, F. R.: Micrococci (staphylococci) enteritis as a complication of antibiotic therapy: Its response to erythromycin. *Proc. Staff Meet. Mayo Clin.*, 28: 121, 1953.
22. SZYBALSKI, W.: "Natural" and "artificial" penicillin resistance in staphylococcus (*Micrococcus pyogenes* var. *aureus*). *Antibiotics and Chemotherapy*, 3: 915, 1953.
23. SPINK, W. W., AND FERRIS, V.: Penicillin-resistant staphylococci: mechanism involved in the development of resistance. *J. Clin. Invest.*, 26: 379, 1947.
24. DEMEREC, M.: Production of staphylococcus strains resistant to various concentrations of penicillin. *Proc. Nat. Acad. Sci.*, 31: 16, 1945.
25. CZEKALOWSKI, J. W.: On penicillin inactivators and susceptibility of microorganisms to penicillin. *Edinburgh M. J.*, 62: 281, 1950.
26. MCGUIRE, J. M., BUNCH, R. L., ANDERSON, R. C., BOAZ, H. E., FLYNN, E. H., POWELL, H. M., AND SMITH, J. W.: "Ilotycin," a new antibiotic. *Antibiotics and Chemotherapy*, 2: 281, 1952.
27. HAIGHT, T. H., AND FINLAND, M.: Laboratory and clinical studies on erythromycin. *New England J. Med.*, 247: 227, 1952.
28. HEILMAN, F. D., HERRELL, W. E., WELLMAN, W. E., AND GERACI, J. E.: Some laboratory and clinical observations on a new antibiotic, erythromycin (ilotycin). *Proc. Staff Meet. Mayo Clin.*, 27: 285, 1952.
29. HAIGHT, T. H., AND FINLAND, M.: Resistance of bacteria to erythromycin. *Proc. Soc. Exp. Biol. and Med.*, 81: 183, 1953.
30. HAIGHT, T. H., AND FINLAND, M.: Observations on mode of action of erythromycin. *Ibid.*, 81: 188, 1952.
31. TANNER, F. W., ENGLISH, A. R., LEES, T. H., AND ROUTIEN, J. B.: Some properties of magnamycin, a new antibiotic. *Antibiotics and Chemotherapy*, 2: 441, 1952.
32. MILLER, J. H., McDONALD, R. R., AND SHOCK, N. W.: The effect of bacitracin on renal function. *J. Clin. Invest.*, 29: 389, 1950.
33. BRYER, M. S., SCHOENBACH, E. B., AND BLISS, E. A.: Pharmacology of polymyxin. *Ann. N. Y. Acad. Sci.*, 51: 935, 1949.
34. SCHNEIERSON, S. S., AND BRYER, M. S.: The importance of the laboratory in antibiotic therapy. *J. Mount Sinai Hosp.*, 20: 155, 1953.
35. BENEDICT, R. G., AND LANGLYKKE, A. F.: Antibiotic activity of *Bacillus polymyxa*. *Soc. Amer. Bact. Abstr. of Proc.*, 24, 1947.

36. STANSLY, P. G., SHEPHERD, R. G., AND WHITE, H. J.: Polymyxin: A new chemotherapeutic agent. *Bull. Johns Hopkins Hosp.*, 81: 43, 1947.
37. AINSWORTH, G. C., BROWN, A. M., AND BROWNLEE, G.: "Aerosporin," an antibiotic produced by *Bacillus Aerosporus* (Greer). *Nature*, 160: 263, 1947.
38. BROWNLEE, G.: Antibiotics derived from *Bacillus polymyxa*. *Ann. N. Y. Acad. Sci.*, 51: 815, 1949.
39. MOREHEAD, R. P., FISHMAN, W. H., AND ARTOM, C.: The nephrotoxic action of dl-serine as related to certain dietary factors. *Amer. J. Path.*, 22: 385, 1946.
40. YOW, E. M., AND MAYER, J. H.: Toxicity of polymyxin B, II. Human studies with particular reference to evaluation of renal function. *Arch. Int. Med.*, 92: 248, 1953.
41. LIEBERMAN, D., AND JAWETZ, E.: Treatment of chronic shigella infection in children with oral polymyxins. *Pediatrics*, 8: 249, 1951.
42. POTI, E. J., MARTIN, R. G., FROMM, S. M., WISE, R. I., AND HSIANG, C. M.: *Texas Reports Biol. and Med.*, 9: 631, 1951.
43. TENG, P.: *Neurology*. In press.
44. GOLDIN, M.: Induced resistance in vitro of *pseudomonas aeruginosa* to neomycin and streptomycin. *Antibiotics and Chemotherapy*, 3: 881, 1953.
45. REGNA, P. P., AND MURPHY, F. X.: The isolation of neomycin B. *J. Amer. Chem. Soc.*, 72: 1045, 1950.
46. TENG, P., AND MELENEY, F. L.: The treatment of intracranial and cranial suppuration with reference to the local and systemic use of bacitracin. *Surgery*, 33: 321, 1953.
47. JOHNSON, B. A., ANKER, H., AND MELENEY, F. L.: Bacitracin: A new antibiotic produced by a member of the *B. subtilis* Group. *Science*, 102: 376, 1945.
48. FUSILLO, M. H., NOYES, H. E., PULASKI, E. J., AND TOM, J. Y. S.: Antimicrobial spectrum and cross resistance studies of erythromycin and carbomycin. *Antibiotics and Chemotherapy*, 3: 581, 1953.
49. WELCH, H.: Editorial, about the chemically descriptive generic terms for aureomycin (chlortetracycline) and terramycin (oxytetracycline). *Ibid.*, 3: 659, 1953.
50. MINTZER, S., KADISON, E. R., SHLAES, W. H., AND FELSENFELD, O.: Treatment of urinary tract infections with a new antibacterial nitrofurantoin. *Ibid.*, 3: 151, 1953.
51. HUNTER, T. H.: Speculations on the mechanism of cure of bacterial endocarditis. *J. A. M. A.*, 144: 524, 1950.
52. WACHSTEIN, M.: Nephrotoxic action of dl-serine in the rat. II. *Arch. Path.*, 43: 515, 1947.

PSYCHODYNAMIC DISTURBANCES IN PATIENTS WITH TEMPORAL LOBE DISORDER*

MORTIMER OSTOW, M.D.

In the text books of psychiatry, the psychic consequences of organic brain disease are usually given as delirium or dementia. A third category is often listed as "epileptic psychoses." In this category are included cases of psychosis among patients with epilepsy, and also patients with brief episodes of psychosis, sudden in onset and sudden in cessation. However, it has been known for many years that psychoses and psychoneuroses, not typically organic in type, are occasionally encountered among patients with organic brain disease. There is, for example, extensive literature on the subject of psychic changes with brain tumor, reviewed recently in great detail by Schlesinger (1).

Hughlings Jackson (2) directed attention to the fact that one component in the developmental sequence of a seizure might be purely psychic in nature, sometimes affective, sometimes a sensory illusion, and sometimes an hallucination. Automatism, i.e. repetitions of stereotyped performances, were also encountered. In 1939, Davidoff (3) reported a case of a young man with post-traumatic seizures. Each seizure consisted of "momentary blankness followed by thoughts of death running through his mind. These occur about three times a week and last the better part of the day. While they last, he is drowsy and inattentive but goes on doggedly with his work . . . if they appear in the evening, he can go to sleep and wake up the next morning with these thoughts still racing through his mind. . . . The thoughts of death may be referable to himself, his mother or other people but are persistent and cannot be diverted no matter how hard he tries to substitute other thoughts. These episodes cease abruptly, the thoughts suddenly terminate, and the patient has an unusual sense of freedom and well-being." The electroencephalogram showed suggestive slowing over the left temporal and central region.

In 1941, Penfield and Erickson (4) classified the psychic manifestations of seizures into four groups. The first, called dreamy state seizures, included illusional seizures and hallucinatory seizures. Petit mal seizures comprised the second group. The third group was automatism, which was divided into two subgroups, post-ictal automatism and ictal automatisms. The fourth group was listed as psychotic states (secondary to repeated seizures).

The cases illustrating this last group were cases of major psychosis, which in at least two cases resembled schizophrenia rather than the psychoses seen with organic brain disease. Penfield and Erickson distinguished these psychotic states from periods of automatism and attributed them to the results of "brain change produced by the seizures." All of these cases showed frontal localization of electroencephalographic abnormalities.

* From the Departments of Neurology, The Mount Sinai Hospital and Beth Israel Hospital, New York City.

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Psychical seizures, except those of the petit mal type are related more definitively to the temporal lobe according to Penfield and Rasmussen (5). They said "the organization of the temporal cortex is evidently different from that of other areas, inasmuch as here alone electrical stimulation and epileptic discharge activate acquired synaptic patterns. The fact that it is only in this region that such stimulation produces complex psychical illusions and hallucinations argues for some degree of localization of intellectual function." In 1944, Pacella, Polatin and Nagler (6) pointed out that in many patients with obsessive compulsive neuroses but without evidence of any organic disorder (other than epilepsy in some), the electroencephalogram showed the bilaterally synchronous paroxysmal slow activity as seen in patients with idiopathic epilepsy. In 1950, Gibbs (7) called attention to the fact that among patients with psychomotor seizures associated with focal abnormality in the anterior temporal region one often encountered "psychiatric disorder which takes the form of personality disturbances and even psychoses. Though such disorder is more or less constant for a given patient, no single specific psychiatric syndrome is encountered. . . . For example, the patient may be paranoid, depressed, catatonic or hysterical. These psychiatric syndromes are a real and an important part of the clinical disorder and may overshadow the epileptic manifestations to such a degree that the patient is diagnosed on a symptomatic basis as schizophrenic or depressive."

It is the purpose of this presentation to investigate the nature of the psychic disorders accompanying organic disease of the temporal lobe in several cases and to compare them with the psychic disorders of the non-organic type.

PRESENTATION OF CASES

Case I. A 64 year old professional man complained that during the preceding year his usual temper-tantrums had become much more violent and more unprovoked than ever. There may have been some impairment of memory. For several months, the patient's driving had become quite erratic, his speed varying from 65 m.p.h. to 20 m.p.h. without his being able to notice the changes. A few weeks before examination the patient had fallen unconscious, with complete amnesia for the attack. Intellectual functions, including orientation, were somewhat impaired, and the patient's vocabulary was considerably restricted. Neurologic examination revealed slight right central facial weakness. An electroencephalogram (Fig. 1) was reported as follows:

Frequency regulation; Good.

Alpha: 9-10 per second; occupies about 95% of the record; usual distribution.

Delta: there is a moderate amount of low to moderate voltage, sporadic, serial and paroxysmal 1-3 per second activity, over the left temporal region, maximal anteriorly.

Beta: None.

Hyperventilation produces no change.

Impression: Mild, focal slowing over the left anterior temporal region.

The patient has since had several episodes of loss of consciousness with falling.

(This case is presented with the kind permission of Dr. Harold L. Otto.)

Comment: This is a patient with a mild diffuse encephalopathy, probably arteriosclerotic in origin, who has in addition a localized disturbance of function of the left anterior temporal region. This case is presented to show that a psychic disturbance, such as the illusion in the perception of speed which occurred here,



FIG. 1. A sample of the electroencephalogram described in case I

could appear from time to time without constituting or being a part of a clinically recognizable seizure. Penfield and Kristiansen (8) described a patient in whom an illusion in the perception of speed occurred as the initial phenomenon in the characteristic seizure pattern. In this patient the same disturbance could be evoked by electrical stimulation in the intermediate frontal region. Similarly, olfactory and gustatory hallucinations may occur as ictal phenomena but also may persist as continuing complaints over periods of hours, days or weeks in patients with encephalopathy due to cerebral arteriosclerosis or in some patients with tumors affecting the temporal lobe.

Case II. A 32 year old married man had been well until the age of 21. At that time he noticed that the right side of his face was numb. At operation a right subtemporal meningioma was uncovered, in the neighborhood of the Gasserian ganglion. A year and a half later he noticed weakness of the left hand and foot, as well as diplopia. He was re-operated but there was such extensive regrowth that it was felt that little could be accomplished surgically. Radiotherapy was administered during which all of the patient's complaints disappeared and he felt quite well. He married shortly afterwards, cast about for employment, borrowed money and went into business as a barkeeper. He apparently did rather well, although later he worried lest municipal condemnation of the property on which his store stood would injure the business. At the time of the examination he had two boys, one three years and one six years old.

He had remained symptom free until about six or nine months before examination. Then he first noticed that whereas he had always previously been a sound sleeper, he was now becoming more and more sensitive to noises, so that he would awaken several times a night in response to external sounds. There was no difficulty in falling asleep. He became more distressed when he began to observe that when standing idly for a moment or two at his bar, the thought of a penis would come to mind, usually with no provocation. He was considerably embarrassed and disturbed by this observation and was even more disturbed

by the observation that the thought of a penis would come to his mind when he was approached by almost any man whom he knew.

A second thought which would thus force itself into his consciousness, without explanation, consisted of a memory of leaving school at a fire alarm at the age of perhaps six or seven because the adjoining building was about to collapse. This memory occurred not only spontaneously, but also when he was with friends with whom he was accustomed to reminisce about his childhood. Of these two forced thoughts, the second occurred much less frequently than the first and, of course, was much less embarrassing to him. The patient has observed no phenomenon which could possibly be called convulsive or ictal in any sense.

An attempt to explore the patient's past history and current psychic state rather extensively was limited by the fact that the patient was rather inarticulate. He recalled no unusual behavior during childhood: no enuresis, no fears, no feeding or sleeping disturbance, nor any other indicators of neuroticism in childhood. The patient had always been on good terms with his parents and was proud of the fact that he had set his father up in business several years ago. He is on good terms with his older brother and, in fact, when there is any friction in the family, he acts as peace-maker.

His adolescence and early maturity had not been marked by any unusual behavior. He occupied himself with finding a proper vocational niche. He married a girl who is apparently stable and reliable and he claims that he is quite fond of her. His only complaint is that she is not adequately responsive sexually and, in fact refuses to permit intercourse more often than once a week. He is unhappy about this particular aspect of their relationship, but is so fond of her that he does not entertain any thought of extra-marital relations. On one occasion when he did attempt such a relation, his guilt feelings made it so unpleasant that he never repeated the experience. He is also somewhat dissatisfied because his wife will not use a diaphragm, so that sexual intercourse is terminated regularly by withdrawal. The patient is perhaps somewhat concerned about the effect of coitus interruptus on his physical well-being. Nothing adverse can be said about the patient's occupational adjustment. Apparently he plays the difficult roles of bartender and proprietor in a rather rough and not always pacific neighborhood with some success, despite his limited intellectual and cultural endowments. The patient works hard from 9 o'clock every morning to midnight every night, without assistance except for occasional relief for an hour or two provided by his wife. He seems to be careful, clean and meticulous about the way he keeps his store. He has had no serious external interests, and during his free time he prefers to read the paper or look out of the window at passers-by. Once a week, or once every two weeks, he will meet some neighborhood friends for a card game.

A recent electroencephalogram (Fig. 2) showed the following characteristics:

Frequency regulation: Fair. Amplitude regulation: Good.

Alpha: 9-11 per second; occupies about 90% of the record; usual distribution.

Delta: a. there is a large amount of moderate to high voltage, sporadic, and serial 1-3 per second activity over the right temporal region, extending up to the right frontal region. b. in addition to this, there is an independent focus of high voltage, sporadic slow waves (1-3 per second) and fast and slow (0.2 seconds) spikes at the tip of the right anterior temporal lobe.

Beta: there is a moderate amount of moderate voltage, regular, serial 12-15 per second activity at the motor and anterior temporal electrodes in transverse leads.

Hyperventilation evokes first an increase in the right anterior temporal slowing and later, several high voltage, bisynchronous bursts of 1-3 per second activity, persisting for about 20 seconds after cessation of hyperventilation.

Impression: a. irritative focus of abnormality at the tip of the right anterior temporal lobe; b. focus of moderate slow abnormality over the right temporal region.

When the electroencephalogram was recorded during conversations, it was found that the appearance of spikes and slow waves was related to the affective content of the patient's utterances. This experiment is described in detail elsewhere. (Ostow (9)).

(This case is presented with the kind permission of Dr. Ira Cohen.)

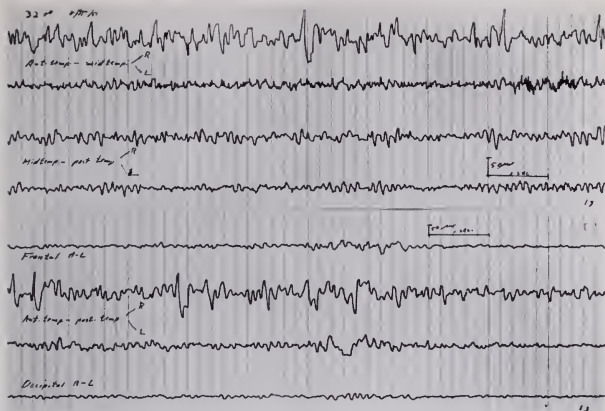


FIG. 2. A sample of the electroencephalogram described in case II

Comment: In this case obsessional thoughts recur at frequent intervals, but are not ictal in nature. There are no other indicators of an obsessive-compulsive neurosis, and these symptoms do not interfere with the patient's work. As is usually the case with obsessions, the idea is considered alien to the patient's conscious ego. He felt they were forced upon him by some agency over which he had no control. Yet the fact that he responded with guilt and that he was much relieved when assured that he should not hold himself morally responsible for them, indicates that he did consider himself guilty about them, at least to a certain extent. The degree to which these thoughts became integrated into the patient's psychic life is indicated by the fact that the ideas occurred not only spontaneously but also as a response when the patient was exposed to certain specific and clearly relevant sensory experiences. In the case reported by Davidoff (3) and mentioned above, there were similar obsessive and fairly stereotyped thoughts accompanied by appropriate affects occasionally persisting for several hours, yet not interfering extensively with the patient's work. From the case just presented and from the case of Davidoff, one may infer that one or more stereotyped ideas may become pathologically active in the sense of presenting themselves frequently and forcefully to consciousness and of not being removable by conscious effort, and that such ideas may become integrated into the psychic life of the patient. These ideas are accompanied by appropriate affects. When the ideas become active they need not be associated with other seizures and they need not be accompanied by impairment of consciousness. This phenomenon seems to be the non-ictal equivalent of what Penfield and Kristiansen (8) called "forced thinking" as a component of seizures. (In their cases, however, at oper-

ation the site of maximal electrical abnormality was usually found to lie in the frontal lobe.)

Case III. A 36 year old unmarried woman was admitted to the Mount Sinai Hospital in December, 1950, complaining of episodes of unconsciousness over the past year and a half. About five years before admission the patient had had an upper respiratory infection accompanied or followed by a sensation of "buzzing" in her ears. A tonsillectomy was performed although both tonsils and adenoids had been removed 20 years previously. Probably because the upper respiratory difficulties did not respond satisfactorily, a left myringotomy was performed. Immediately following this procedure the patient claims to have become unconscious and to have remained so for about an hour to an hour and a half. The procedure was extremely painful. The following day she said the buzzing in both ears became more severe and it has persisted since that time. When telling the story on other occasions the patient insisted that the left ear is the site of louder and more disturbing noise than the right. The sensation of noise in fact spreads at times from the left ear all over the left side of the head, and at times the left side of her head becomes numb. At other times there is a sensation of heaviness on the top of the head. About a year and a half before admission the patient began to have a series of "blackouts". Apparently these are seizures which consist of impairment or loss of consciousness lasting from about 30 seconds to four or five minutes, without falling. Sometimes at the beginning of an attack she will say, "Leave my ear alone" or "Don't do it". She makes scratching movements, and on one occasion she was observed to scratch her right ear hard enough to make the external ear bleed. At times there is unintelligible mumbling and often drooling. On one occasion flushing of the face was seen. During the attacks observed in the hospital, the period during which the patient was actually out of contact was less than a minute, but this was always following by three or four minutes of lethargy and drowsiness.

During the past five years there has also been a rather profound psychic change. It is known that about five years before admission, (that is about the time of the myringotomy and the initial episode of unconsciousness), the patient consulted a psychiatrist for a period of about six months because of her concern over recurrent dreams about her mother, who had died seven years previously. With the onset of these dreams, she restricted her social contacts sharply and for the past year and a half had had no social contacts at all. She gained a good deal of weight during the same period of time. At one point during the past five years she developed the idea that the doctor who had performed the myringotomy had actually injected a large amount of brown fluid into her left ear through a long needle. She believed that the needle was too long, that he had struck a nerve inside her left ear which in turn caused the noise in her ear ever since. This operation she says is also responsible for changing the color of her hair to grey and for a gain in weight from 128 to 171 pounds, both within the course of one week immediately following the operation. Her sisters have also adopted this belief. She denied any genital sexual experiences. About three years ago she formed a relation with a young man which she thought might end in marriage. On one occasion she said she dropped him because of her illness. On another occasion she said that the man's employer told him not to marry a girl who had no parents.

On admission to the hospital, examination disclosed a myringotomy scar in the left ear, lateralization of the Weber on the left, impairment of hearing on the left with bone conduction better than air conduction and no abnormal findings on neurologic examination. A virginal introitus was consistent with the patient's denial of genital sexual experience. X-ray of the skull was normal. An electroencephalogram performed on December 15th (Fig. 3) was reported as showing "a fair amount of delta activity with frequencies as low as 1.5 cycles per second appearing at the right ear lobe and inferior frontal electrodes. There are many sleep patterns. Spikes appear frequently at the right ear lobe electrode, sometimes spread to the left ear electrode and to the right inferior frontal and occipital electrodes. They are most frequent in the superficial stages of sleep." *Impression:* focal irritative lesion in the right temporal and inferior frontal (anterior temporal) region. A

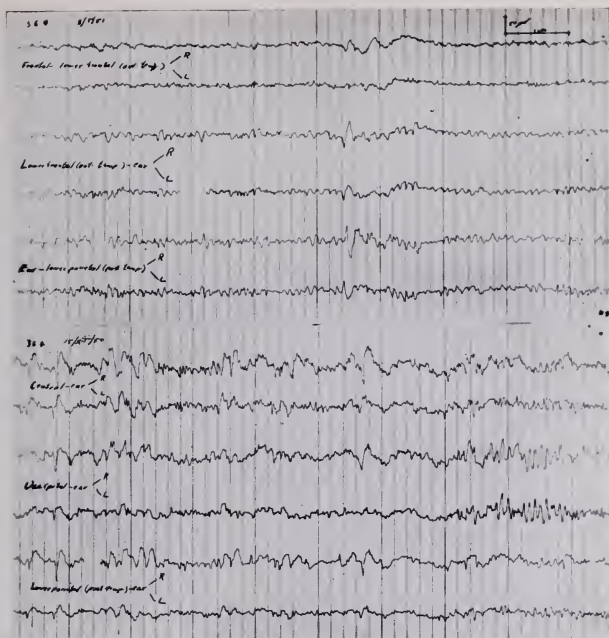


FIG. 3. Samples of the electroencephalograms described in case III

second electroencephalogram was performed on the 3rd of January 1951 and the report read "A low amount of delta activity with frequencies as low as 2 cycles per second appears at the right inferior frontal electrode. There are a few symmetrical and diffuse bursts of mixed frequencies from 3 to 6 cycles per second. Single spikes appear at both ear lobe electrodes, more often on the right side." *Impression:* This record is less abnormal than the previous one but again indicates a focal lesion in the right inferior frontal-temporal region. Pneumoencephalography and cerebral angiography on the right failed to disclose any evidence of abnormality.

On the 26th of December 1950 one hundredth of a grain of hyoscine was administered subcutaneously and 10 grains of aspirin orally in preparation for pneumoencephalography. The patient became agitated and even after the injection of 15 grains of sodium amytal intravenously, she was so active that it became impossible to perform the pneumoencephalogram. She remained excited that day and at night she complained that the doctor who had performed the aural injection five years ago was in the room with her. She pleaded with him not to touch her ear. On the following morning she expressed the wish to die but also asked for reassurance that she would not. The severe psychic disturbance continued for at least two days. At times she exhibited unwarranted happiness and at others reduced activity. On the 10th of January pneumoencephalography was successfully performed and

the patient showed no adverse reaction except for headache which she localized to the ears. On the following day, 7½ grains of sodium amytal were injected intravenously. The patient "became very excited, sitting up and crying. She loudly called upon her mother's ghost to tell her that she had really been made sick by the ear injection; that it had caused her blackouts, tinnitus, loss of good looks and the greying of her hair. She further stated that the otolaryngologist's office nurse was discharged because she took the patient's side . . . (she) also expressed horror when shown a hypodermic syringe, although she hadn't before amytal." On the 19th of January percutaneous arteriography was performed without adverse reaction by the patient. There were no abnormal findings. After having had phenurone for about 12 days the patient showed a diffuse papular eruption. Pneumoencephalography was repeated on the 26th of January. The patient was restless and co-operated poorly. Immediately afterwards she became agitated and remained so for two or three days. She was somewhat assaultive and she addressed her dead mother by name but denied seeing or hearing her. She showed no disorientation for time, place or person. She believed that the recent procedure was not a pneumoencephalogram but "something was done to my ear". She was noisy and demanding.

A week later she was transferred to the psychiatric service and at about the same time regained her initial composure. She was observed to be boisterous, loud and provocative. She belched frequently and claimed that this was a new symptom. She complained of a bad odor in her mouth. She cried frequently while talking to the psychotherapist and complained that the doctors didn't believe that her noises were caused by an injection. With a good deal of emotional turmoil she revealed that a 19 year old niece was hospitalized because she was mentally retarded and spastic. She did not talk very easily and soon became impatient to go home. She planned to dress up nicely at home and to resume wearing earrings. She said she began to wear earrings about 12 years ago and took them off on three occasions. The first was when her mother died, the second when her niece was hospitalized and the third when she developed the trouble with her ear. She had not worn them since that time, that is during the past five years. She stopped cutting her hair about 5 years ago too and would not go to a beauty parlor until a year ago. Since the onset of her current symptoms the patient has worn a kerchief on her head rather than a hat. However, while on the psychiatric ward she had a dream that her mother told her to stop wearing kerchiefs. This the patient took to be a sign that she was going to be well and she resolved that when she got home she would wear a hat again. Because of the patient's social withdrawal and because of her hypochondriacal delusions, the diagnosis of paranoid psychosis was made on the psychiatric service.

The patient was seen again in January, 1952. She was taking dilantin. An electroencephalogram was entirely normal. The focal slowing and spike activity seen in earlier records was not found but the patient was not drowsy. She had been feeling relatively well and was aware of no seizures. Moreover, she had been less seclusive and depressed. She had been working at a new job, had resumed social activities and was no longer preoccupied with her delusions—although questioning readily elicited their presence.

Comment: In this case we can see at least two problems. The first is a severe psychic disturbance resembling a paranoia or a paranoid schizophrenia active over a period of at least five years. The second consists of a series of seizures observed over a period of a year and a half probably related to a focus of slow waves and spikes over the right temporal region. Although one might argue that these are two discrete processes only fortuitously related in this case, the fact that the patient's seizures usually began with protests not to touch her ear and with scratching movements directed towards her ear or against an aggressor, means that the same psychic fantasy is expressed both in the patient's seizures and in her psychotic delusions.

If we were to treat the two processes as independent we should not know to which we should ascribe the following symptoms: belching, the bad odor in the mouth, and the tinnitus principally in the left ear. Penfield and Kristiansen (8), mention three patients each with a lesion of the first temporal gyrus on one side, and each of whom described auditory sensations at the onset of a seizure. These sensations were described as a "roaring in the ears" or "a plane going by." Penfield and Erickson (4) describe a patient who had a post-operative meningo-cerebral cicatrix affecting the tip of the left temporal lobe. In her attacks she heard voices or music coming from her right.

It is interesting to note that the patient considered her seizures, including the remarks and gestures concerned with warding off an attack on her ear, as alien to her and imposed from without, a disease of which she had to be cured. On the other hand, her hypochondriacal delusions she considered to be real and valid, i.e., conclusions which any reasonable person would reach. This contrast is perhaps most aptly expressed by the psychoanalytic terms, ego-alien and ego-syntonic respectively. The three periods of excitement in which the patient's delusion that she had been attacked through her ear were replaced by a fear that she was about to be attacked were induced by the administration of drugs, and on two of these occasions by the physical procedure of pneumoencephalography (or the attempt in one case) as well. The physical procedure she misinterpreted as a real attack on her ear. Nosologically, the episodes might be considered acute schizophrenic excitements, acute deliria or toxic drug reactions. Descriptively, one might say that the drugs acted to impair her reality testing and thereby permitted her ever active fantasy of an aural attack to assert itself as a present danger. Although psychiatric investigation was not sufficiently thorough to reveal to us either the genetic origin of her fantasy or even a good picture of the fantasies themselves, some central areas of concern are evident. The principle concept, of course, is the attack on her ear. Associated with this is the problem of whether the ear should be adorned with the earrings. The earrings were removed when the mother died and the patient's niece was hospitalized as well as when she herself became ill. The care of the hair, the wearing of hats as opposed to kerchiefs are also problems related to and derived from these fantasies. The fact that the mother played a part in these fantasies is indicated by the recurrent dreams in which the mother gives the patient permission to do one thing or another. Since the fantasy through its derivatives pervades so many aspects of the patient's life, and since it is closely related to her ideas and feeling about her mother, one may safely infer that it was formed early in childhood. One may ask about the nature of the relation between the temporal lobe abnormality and the psychic disturbance. Was this fantasy dominant for psychogenic reasons and did it become associated with temporal lobe seizures merely because it was dominant at the time the temporal lobe abnormality developed? Or did the temporal lobe abnormality by virtue of its anatomic location make this particular fantasy pathologically active?

The importance of this case is its demonstration that the same fantasy may be an integral part of a temporal lobe psychomotor seizure, and simultaneously a nodal point in an extensive psychodynamic system.

In the following case there are recurrent brief episodes which can be interpreted either as true psychic seizures or as anxiety attacks.

Case IV. A 38 year old man complained that one morning he had suddenly felt an unusual sensation which comprised a feeling of "sinking" apprehension, together with a sense of finality. . . . Simultaneously, he felt as though he were being struck in the head, in just about the midline. The attack produced a good deal of fright but lasted no more than a few seconds. He felt that he had to struggle to retain consciousness. It was learned later that the attack was associated with a feeling of depersonalization. He had had two such attacks on the day on which he first reported for examination, but none previously. He had been aware of headaches for the previous six months. The patient had had no similar experiences in the past. He was seen again on the following day but the same sensation did not recur until the patient began to talk about the attacks of the previous day. He remembered that two years before, he had found himself becoming so preoccupied at times as to be unable to do his work. The preoccupation was concerned with the thought that his wife might be unfaithful to him and with reminiscences of the past. There was no relevant family history and no significant past history of illness except for an orchitis due to mumps at about the age of 4, which resulted in the atrophy of one testis.

Neurologic examination: cranial nerves were normal. Optic disks were clearly demarcated. Pupils were equal and responded well. All motor and sensory functions were normal. Deep tendon reflexes were perhaps slightly underactive but symmetrical. Superficial reflex pattern was normal. An electroencephalogram (Fig. 4) was performed on the day after onset of these attacks and was reported as follows:

Frequency regulation and amplitude regulation: Fair.

Alpha: 9-11 per second; occupies about 85% of the record; usual distribution.

Delta: there is a small amount of low to moderate voltage, sporadic 3-6 per second activity at both temporal regions, most prominent at left posterior temporal electrode; occasionally with spike-like components and more prevalent as drowsiness begins.

Beta: None.

Hyperventilation produces slowing to high voltage bursts of 2-3 per second waves with spike-like components arising from either or both temporal regions, more often from the left, sometimes anteriorly, sometimes posteriorly; this slow activity persists for 1½ minutes after hyperventilation and is associated with subjective dizziness and apprehension.

Impression: There is focal slowing in both temporal region, more pronounced on the left.

Careful ophthalmologic and perimetric examinations disclosed no abnormality of vision or visual fields. The patient was referred for psychotherapy and has been seen about twice a week for a period of about a year. The patient's attacks, which were interpreted by the psychotherapist as anxiety attacks, recurred several times a day at first but after a few months diminished in frequency and intensity so that at present they occur no more than two or three times a month on the average and in each instance in response to some environmentally imposed difficulty. He continued to have a good deal of concern about his wife's supposed infidelity. It was based upon the fact that ten years earlier when they were first married, they had some differences and she left him for several months. At the time she had given him the impression that she had gone to live with another man, but she told him later that this was not so. He had accepted the amended version of the story until two years ago, when he consistently began to misinterpret irrelevant events as indications that his wife was continuing to be unfaithful. At times the reasoning he used to sustain this belief was bizarre and elaborate. In addition, there were ideas of reference. At times the patient felt that he was under electrical control by external agents and said that the sensations which he recurrently felt in the middle of his head were really electric shocks. He wondered whether people were hypnotizing him. The feelings of depersonalization which came on with the anxiety attacks sometimes persisted for several hours. During the course of treatment there were numerous anxiety dreams dealing in every case with a

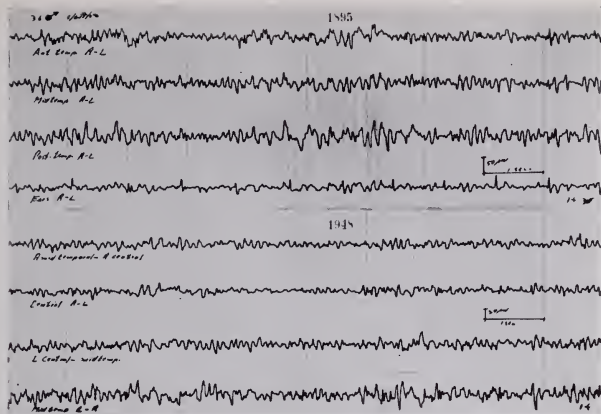


FIG. 4. A sample of the electroencephalogram described in case IV

physical attack upon himself. For example, in one dream the patient's father cleaved him in half with an axe, starting from the crotch and going up. The patient suggested that the shocking sensation he felt in the midline of his head might actually be an upward displacement of the fantasy of being hit in the genitals with an axe. While in treatment the patient, a skilled craftsman, left his job and soon found another one. He had trouble with his employer, which he was able to handle with the assistance of psychotherapy. As difficulties with his employer and his wife were worked through successively, the intensity of his symptoms diminished, so that he now is able to work successfully and to make at least a passing adjustment with his wife and two children.

It is difficult to determine exactly the time of onset of this mental illness. The patient had been enuretic until relatively late, but there were few other indicators of neuroticism. On the basis of the material which became available during psychotherapy, it was felt that the patient's delusions were based upon projections of homosexual feelings. These are supposed to have included doubts of his own virility and subsequent compensatory masculine strivings. It was felt by the psychotherapist that this was a case of paranoid schizophrenia without any atypical features.

(This material was made available by Dr. Lionel Ovesey and is published with his permission and that of Dr. Selvan Davison.)

Comment: The most interesting feature of this case is the series of attacks which might be described either as focal seizures or as anxiety attacks. The components of fear, depersonalization and peculiar cephalic sensation may occur in either. Since there were no seizures during the actual electroencephalographic recordings, the distinction was never made in this case. It is noteworthy that the patient incorporated the fact of the seizures into his paranoid delusions. Moreover, the psychotherapist could assign a specific psychodynamic role to the seizures. Their incidence and severity were diminished *pari passu* with the total psychic disturbance, under the influence of psychotherapy.

One possible explanation of the fact that a clinical picture could be organic

and/or psychogenic in origin is that the clinical picture is the result of the activation of a given neural mechanism and that both psychic processes and organic irritation have access to and can activate this mechanism. This is an inference already suggested by cases II and III. The same explanation might be appropriate for the repetitive dreams occurring before a seizure in patients having focal seizures. The obsessive delusion and reminiscences which preceded the onset of the spells resembled the obsessive thoughts encountered in case II. Case IV also resembles case III in exhibiting seizures and a delusional system. In case IV the seizures are considered ego-alien and are treated by projection, as the effect of a malevolent influence. As in case III however, the delusions themselves are ego-syntonic.

DISCUSSION

It has been demonstrated in the case material presented above that psychic disturbances may be encountered among patients with temporal lobe disease in the following forms: (1) as one of a sequence of components of a seizure; (2) as the sole component of a seizure; (3) episodically but not as a seizure (that is, without abrupt beginning or ending and without disturbance of consciousness); (4) as a fairly constant disturbance sometimes more, sometimes less prominent. These psychic disturbances are sometimes considered to be ego-alien, especially the first two forms, and sometimes ego-syntonic, especially the last form. All of the ego-syntonic phenomena and even some of the ego-alien phenomena become incorporated into the psychic life of the patient. They may be elicited by appropriate psychic, external stimuli. One or more derivatives of a conscious or unconscious fantasy may appear. Defensive attitudes or manoeuvres become evident. As a result of this incorporation into and integration with the psychic life, the clinical picture comes to resemble that of neurosis or non-organic psychosis so closely as to be distinguishable only with difficulty. The finding of electroencephalographic abnormality can only be of suggestive value. For example, in case II, it was only the historical development and in case III, the appearance of the central fantasy of the delusion in actual seizures, which permitted the identification of the disturbance as organic in origin. The question which we must ask then is: how is it that an organic lesion of the temporal lobe is so apt to give rise to a psychic disturbance indistinguishable from neurosis or non-organic neurosis?

Before attempting to answer this question, it will be useful to review briefly one aspect of the psychoanalytic theory of neurosis. According to psychoanalytic theory, a neurosis is the consequence of imperfect repression of an unconscious drive. An unconscious drive is a drive which deals with such primitive activities as nutrition, excretion, aggression and expression of and request for love, either singly or in combination. The whole gamut of these drives which are operative during adult life become active before the age of 5, in some instances even during the first year. For this reason the earliest and most primitive expression of such a drive is formulated in terms with which the infant is familiar. The anatomy of the individual is expressed in terms of surfaces, appendages and apertures.

Humans are not distinguished from each other or from animals. Parents are endowed with strange and exaggerated powers and wishes. With this infantile material, the infantile drives form fantasies in which the drives are expressed as wishes. As the child continues to develop, it seems to him that the expression of such wish fantasies would result in terrifying situations. Moreover, he feels all of this to be looked upon with disfavor by his parents. For both reasons, the process of repression sets in. The result of this repression is that the infantile fantasies, that is, the infantile formulations of instinctual drives, are not permitted to remain conscious. How then do instinctual drives express themselves? Some post-infantile experiences, expressed in rational adult terms, begin to acquire a subjective importance which seems objectively inappropriate. Briefly, a conscious rational wish fantasy becomes substituted for the infantile and now unconscious fantasy. Usually a single unconscious fantasy will give rise to several conscious fantasies. These are considered to be derivatives of the unconscious fantasy. A classical example is the familiar development of a fear of animals. A child has a strong desire for loving contact with his father and yet fears that such contact may result in physical damage to himself. Such a fear if expressed directly would preclude any kind of relationship with the father. Dogs however are known to be dangerous to little children. By repressing the ordinarily intense love for the father and fear of the father and substituting a friendly working relation with the father and a fear of dogs, the child is able to continue his expectation and appreciation of love from his father. The exaggerated fear of dogs is then a derivative of the desire for and fear of love from the father. There will of course be many other derivatives of the same fantasy, for example: certain irrationally intense feelings about male teachers, supervisors and friends. The process of repression is supplemented and supported by other defensive manoeuvres such as denial, projection, reaction formation. To the extent to which the conscious derivatives of unconscious fantasies are satisfactory substitutes and give rise to constructive desires and ambitions, and to the extent to which the defenses do not result in too great a burden of irrationality, repression is successful and the individual is free from neurosis. When the process of repression is imperfectly accomplished, inappropriate and unsophisticated derivatives, and obstructing defenses produce neurotic symptoms and personality distortions. Whether the partial failure of repression is caused by a defect in the mechanism of repression itself or by pathologically strong activity of the unconscious fantasy is a distinction which we do not know how to make at this point. In summary then, according to psychoanalytic theory, a neurotic (or for that matter, psychotic) symptom appears when an unconscious fantasy is not successfully repressed so that derivatives of this fantasy give rise to irrational behavior and defenses against the fantasy and the derivatives disrupt normal personality function.

Returning now to the question of the resemblance between the psychic consequences of temporal lobe disease and the neurosis and psychosis of nonorganic origin, we may propose the following thesis: some kinds and distributions of temporal lobe disease may confer pathological overactivity upon one or more

unconscious fantasies so as to preclude adequate repression, or they may interfere with the repressive mechanism itself. In either case, the consequence will be imperfect repression of an unconscious fantasy and according to psychoanalytic theory, this should give rise to neurosis or psychosis.

What evidence may be adduced in support of this thesis? The defense of this thesis derives essentially from a comparison of the effects of abnormal temporal lobe activity with the phenomena of neurosis and psychosis. On the most elementary level such phenomena as sensory illusions, depersonalization, *deja vu*, dream like states, hallucinations and anxiety, depression and other affects are characteristically seen in each condition so that in some instances, such as in case IV, the clinical phenomena alone do not permit a distinction between the two. In addition, the automatisms seen either during or after some psychic seizures (especially those called psychomotor) are behavior fragments, often stereotyped in a series of seizures, which could easily pass for hysterical episodes, and in the case of the post-ictal automatisms, often pass directly into hysterical fugues without any sharp transition point.

It sometimes happens during the course of a temporal lobe seizure that a patient recalls a specific event from the past or imagines that he is again living through that past event often with intense feeling. At times he is enacting a scene which is not a memory of something past but which might be more appropriate to something current. Such scenes can be stereotyped. In Penfield's protocols one encounters a number of such instances. When the affected temporal cortex was exposed, stimulation could evoke these psychic experiences and others. Now in psychoanalysis too, we often encounter persistent childhood memories some of which carry a surprising amount of affect. We call them "screen memories." We usually ascertain that such memories are substitutes for, and occasionally condensations of, memories of similar experiences from much earlier childhood which have been repressed.

Another important element in this series of psychic productions common to psychoneurosis and to temporal lobe disease, is the dream. Penfield (8) has described cases in which a fairly stereotyped dream would be repeated night after night until, following a number of repetitions, a seizure resulted. The patient might be free from seizures for intervals of several months. However, the recurrence of the dream one night would always presage the appearance of a seizure within a few days. Such dreams or fragments of them, could be evoked by stimulation of the diseased temporal lobe at operation. Penfield and Rasmussen (5) suggested that "Hallucination, dream, and memory depend on the same neuronal mechanism in the temporal cortex." The importance of the dream for the understanding of the psychoneurotic process was investigated in great detail by Freud and his followers. He referred to the dream as "the royal road to the unconscious" implying that in spite of the distortions appearing in dreams, the material of the dream was closer to the raw repressed infantile fantasies than was the product of the waking mind. Repetitive dreams which occur frequently among neurotics and which may presage the return of one symptom

or another are usually found to contain a crystallization of one or more important, unsolved unconscious conflicts. In case III, the patient's difficulties in her relation with her mother were epitomized in her dream in which her mother gave her instructions on proper behavior. Such dreams usually preceded a change in her conscious attitudes. However, they often dealt with the same material which appeared in the seizure, namely the defense against attack by ear. In case IV, the sensations of the seizure were symbolized in dreams as the sensation of a physical attack upon the genitals. One may assume then that a dream can either activate or be activated by either a neurotic process or an organic disturbance. That is to say, it can participate in an organic process in the same way that it participates in the neurotic process.

Fantasies, memories, illusions, hallucinations and dreams are a series of phenomena in which relatively undistorted, usually irrational derivatives of unconscious fantasies break through to consciousness. The responsibility for what they say is often disclaimed by the individual who has them. The rules for undoing the residual distortion so as to arrive at the repressed fantasies were painstakingly worked out by Freud. If the thesis suggested above is correct, then the same rules which apply in the formation of derivatives in the case of the neurotic, should apply also in patients with temporal lobe disease. To ascertain whether this is so, in a really convincing way, one would have to analyze a patient with temporal lobe seizures fairly rich in psychic content or a patient who could be made to yield such material as a result of a temporal lobe stimulation at operation. I suspect that this sort of investigation might be extremely useful but, to my knowledge, it has not yet been performed. Some of Penfield's protocols contain sufficient material to make such analytic interpretations, but I have seen none that contain enough material to verify an interpretation.

Of course the principle evidence which we have to offer in this presentation is simply the demonstration of derivatives and defenses in the cases described above very much as they are seen in psychiatric patients without organic disease. Finally, it is important to realize that as a psychic seizure or its equivalent evolves, one cannot tell whether a subsequent step is a psychic response to the preceding step, whether it is organically activated, or whether it is the result of the unfolding of a memory of a previous sequence. Perhaps in terms of neurophysiology, all of these possibilities are equivalent.

CONCLUSION

From a series of four cases of patients with temporal lobe disease and psychic disturbance, it is inferred that the fragments of disordered behavior seen in brief seizures are identical in appearance and probably in psychodynamic relations with neurotic (and psychotic) behavior of the nonorganic type. It is suggested that this observation can be explained by the psychoanalytic thesis that neurosis arises from unsuccessful repression of unconscious fantasies; presumably some forms of organic disease of the temporal lobe can act either to weaken repression or to reinforce unconscious drives, in fairly specific, narrow areas.

REFERENCES

1. SCHLESINGER, B.: Mental Changes in Intracranial Tumors and Related Problems. *Confinia Neurologica*, 10: 15-263, 322-355, 1950.
2. JACKSON, H. J.: Selected Writings, London 1931.
3. DAVIDOFF, L. M.: Psychic Seizures as Focal Manifestations in Post-Traumatic Brain Disease. *Yale Journ. Biol. and Med.*, 11: 557, 1939.
4. PENFIELD, W. AND ERICKSON, T. C.: *Epilepsy and Cerebral Localization*, Charles C. Thomas, Baltimore, 1941.
5. PENFIELD, W. AND RASMUSSEN, T.: *The Cerebral Cortex of Man*. MacMillan, New York, 1950.
6. PACELLA, B. L., POLATIN, P. AND NAGLER, S. H.: Clinical and Electroencephalographic Studies in Obsessive Compulsive States. *Am. Jour. Psych.*, 100: 830, 1944.
7. GIBBS, F. A.: Ictal and Non-Ictal Disorders in Temporal Lobe Epilepsy. *Jour. Nerv. and Ment. Dis.*, 113: 523, 1951.
8. PENFIELD, W. AND KRISTIANSEN, K.: *Epileptic Seizure Patterns*. Charles C. Thomas, Springfield, 1951.
9. OSTOW, M.: Fluctuation of Temporal Lobe Electroencephalographic Abnormality During Psychic Function. *Am. J. of Psych.*, 110: 55, 1953.

AN INTRODUCTION TO THE PATHOGENESIS OF VIRAL INFECTIONS*

ALFRED L. FLORMAN, M.D.

From the Department of Pediatrics, The Mount Sinai Hospital, New York, N. Y. and the Division of Pediatrics, The North Shore Hospital, Manhasset, N. Y.

Our knowledge of the pathogenesis, or mode of production, of naturally acquired viral infections has increased greatly during the past 10 years, however much still remains to be learned. It will be the purpose of this presentation to outline some of the basic principles which have been elucidated, and to illustrate their workings with specific reference to human diseases.

These basic principles include the following facts: Viruses differ among themselves in size, complexity and potentiality or virulence. Therefore, the particular agent must always be specified. The modes of transmission differ. Some diseases are spread by droplets, others by contact, by water or insects. The reactions of the host differ depending upon his age and state of immunity. Whether an overt clinical or a subclinical infection results depends also upon the virulence and number of infecting organisms. In short, there is no single way in which viral infections are initiated but rather a variety, reflecting mainly the agent and the host.

In approaching the complex problem of pathogenesis it is perhaps easier to start at the end of the cycle and consider first the mechanisms by which infections are overcome and subsequent resistance maintained. This appears to center chiefly about the production of specific antibodies. In his Dunham lectures Burnet (1) summarized the problem: "Broadly speaking, there are three different situations which may develop. (a) Infection may be followed by elimination of the virus and permanent or at least prolonged immunity. (b) Infection persists with repeated opportunities for liberation of the virus despite active antibody production. (c) Infection of mucus surfaces is followed by antibody production and immunity of varying duration." Although these categories are not always sharply delimited, they do provide a good framework for discussion.

In general, infections which produce solid and prolonged immunity involve dissemination of virus through the blood stream. This provides an effective stimulus to the antibody producing mechanisms and an opportunity when reinfection occurs for the virus to be exposed to circulating antibodies before it can reach those cells which are selectively damaged. These are also the situations in which effective prophylaxis is most promising. Measles, mumps and poliomyelitis are common examples of infections which fit into this category.

Mumps is caused by a virus which has pantropic qualities, but which seems to prefer salivary gland tissue. As early as the time of the Hippocratic writings (2) there is a clear description of the parotid swelling associated with this infection. The virus has been recovered from salivary secretions with relative frequency

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and this is presumed to be the usual route of spreading the disease. However it is significant that the virus has been recovered many days before the appearance of obvious signs of disease, and that for the virus to be present in saliva the patient need not ever show parotid or submaxillary swelling (3). It has also been possible to recover the virus from the blood stream (4), which substantiates the concept of a viremia in this infection. There are a variety of immunologic reactions which are initiated by infection with mumps virus. These include the development of neutralizing complement fixing and antibodies which prevent agglutination of red blood cells, and evidence of hypersensitivity as shown by reactions to intradermal testing with material containing killed virus. One of the striking things about these antibodies is that they may appear as early as the onset of first clinical signs (5). Both serologic and skin tests have demonstrated that there are many more instances of subclinical mumps than were previously suspected (6). This helps to fill gaps in our knowledge of the epidemiology of this disease. Nevertheless there are still many unknowns. One of these has to do with the rarity of mumps in the first year of life. Florman, Schick and Scallatar (7) showed that maternal complement fixing and agglutination-inhibiting antibodies passed in relatively undiminished titer from mother to newborn child. If these passively acquired antibodies could be shown to persist for a long time one might better understand this rarity on the basis of passive protection. However, Florman and Karelitz (8) have recently been able to follow a number of infants who at birth had detectable mumps antibodies which persisted for an average of only about 50 days.

Mumps is one of those infections in which immunity following infection is of long duration and, indeed, we have been unable to find any second attacks of mumps which were substantiated in the laboratory. This is also a disease which should theoretically yield to efforts at prophylaxis. Efforts have been made for a long time to achieve this passively without any clear cut results. However, more recent attempts at active immunization using both killed and attenuated chick embryo grown virus have been more promising. In one of the largest and best controlled studies, carried out among Alaskan Eskimos (9), the vaccine appeared to reduce to one half the incidence of mumps among the vaccinated group, even though they had been vaccinated approximately 9 months before the outbreak of the disease.

The data regarding poliomyelitis are very much like the findings in mumps. Although there are at least three types of poliomyelitis virus (10), they are all pantropic in nature, and viremia occurs before the appearance of neurologic symptoms (11, 12). Patients excrete virus before the appearance of obvious clinical signs and so contribute to the spread of the infection. The virus probably enters in most instances by way of the mouth. Although the difficulties in obtaining data in this disease are considerably greater it seems clear that, as in mumps, specific antibodies appear very early in patients with poliomyelitis. Second attacks of poliomyelitis have been reported. It now seems probable that such infections are caused by a type of poliomyelitis virus different from that which caused the original infection for immunity in this disease is type specific

(13). Attempts recently have been made to obtain prophylaxis during the viremic stage with gamma globulin (14). These studies are extremely interesting and are now receiving a limited clinical trial (15). As with mumps, efforts have been made to obtain active protection using tissue culture grown killed virus and attenuated live virus (17). These studies appear promising.

The measles story is not as clearly documented because as yet the human being remains the only reliable experimental animal. Nevertheless, the outline seems to fit the picture given for mumps and poliomyelitis (18). The greater reliability of passive protection in this disease probably reflects greater ease in recognizing the disease, so that time of exposure can be more accurately determined, as well as a probably higher antibody titer in pooled adult serum.

Herpes simplex infection is an example of the second type of situation described by Burnet in which infection persists despite active antibody production. Herpes infection usually occurs for the first time during early childhood. Although antibodies are produced during convalescence, the virus is not eliminated but remains walled off within the infected cells. This represents a successful symbiotic arrangement between host and virus. However, if something happens at a later date to lower the resistance of the host, be it high fever, a gastro-intestinal disorder or even menstruation, the virus may come forth and again produce the characteristic fever blister, despite the presence of circulating neutralizing antibodies. Herpes simplex is usually considered a dermatotropic virus, but it is now appreciated that this agent also has pantropic properties—especially in the very young. Occasional instances of meningitis and encephalitis due to herpes simplex have been reported even in the absence of obvious mucocutaneous lesions (19). More recently Zuelzer and Stulberg (20) have reported hepatitis due to this virus in young infants dying of unexplained fever. Florman and Mindlin (21) have also shown the pantropic properties of herpes simplex in a report of generalized infection in an 11 day old infant who developed skin, mucus membrane, central nervous system and retinal changes. It has also been shown in a few instances that neutralizing antibody is transmitted from maternal to infant circulation in undiminished titer (21, 22). Infection with this virus also stimulates the production of complement fixing antibodies (23) and may induce a state of hypersensitivity (24).

Psittacosis (25) is a second example of a human disease in which the virus has been proven to persist long after recovery. Similar situations have been found with virus affecting lower animals. Salivary gland disease of guinea pigs, lymphocytic choriomeningitis of mice and infectious anemia of horses are such examples.

The third situation described by Burnet in which infection of mucus membranes is followed by antibody production and immunity of varying degrees may be illustrated by influenza and the common cold. Again, as with mumps, influenza is one of the viral infections about which a great deal has been learned as a result of the ready availability of a susceptible laboratory animal and easily preformed serologic tests. The influenza viruses enter by way of the respiratory tract and act as antigens to elicit a variety of antibodies, and a state of hyper-

sensitivity. Resistance to subsequent infection is type specific (26). The 3 known influenza virus types are referred to as A, B, and C. There are also antigenic variations within these types which are in the main quantitative in nature. However, one of the critical factors in resistance to these infections seems to be the level of antibody at the portal of entry, the nasal mucosa, which happens also to be the site of predilection in the human being for infection. Francis (27) has shown that for type A the concentration present in nasal mucus is about $\frac{1}{10}$ to $\frac{1}{20}$ the amount present in blood. It is likely therefore that a good deal more antibody must be produced in the body to protect the mucus membranes than would be needed to neutralize the virus in the laboratory. This probably explains the observation that the mere presence of circulating influenza antibodies is no assurance of protection. The level must be sufficiently high to maintain an effective level at the portal of entry.

Because of the short incubation period of influenza, attempts at passive protection with antisera have not been practical. Similarly because of antigenic differences and the need to maintain high levels of antibody, attempts at active immunization have had limited success in the past. More recently through the use of especially selected strains of virus and with the addition of adjuvants such as described by Salk (28), the prospect for the development of a successful vaccine has brightened.

MacLeod (29) has suggested that it might be possible to divide infectious disease on the basis of length of incubation period, and show that in general those with long incubation periods had long lasting immunity, while those with short incubation periods had immunity of short or variable duration. This concept is based on the thought that the opportunity for effective amnesic or recall response during the incubation period of a second contact with an infectious agent exists only in those diseases with relatively long incubation periods. This is consistent with what has just been discussed.

Complete knowledge is lacking regarding the changes which occur in the cell at the moment of infection, but an approach to this problem has been made. Laboratory studies indicate that there are at least three steps involved (30). The first is the initiation of infection. This is presumably a combination between free virus particles which have been brought to the susceptible cell and some receptor on or in that cell. The second is the latent period during which it is no longer possible to demonstrate even the quantity of virus which was introduced. The third is the period of multiplication during which free virus in increased quantity can be detected. Just what happens during each of these steps remains to be elucidated. However, it has been possible to show that at least for certain viruses such as influenza, mumps and Newcastle disease virus, there are cellular receptors which have been characterized chemically. These are present in the case of influenza on the surface of cells of the respiratory tract of the ferret and on red blood cells. Indeed the red blood cell which can be agglutinated by these viruses has served as a useful laboratory tool for the study of this phenomenon (31). It has been shown that substances analogous to these receptors are present in a number of biological fluids and that they, as well as

the receptors, can be inactivated by certain enzymes. The possibilities inherent in these observations for the chemotherapy of virus diseases by blocking infection at the site of viral receptor or by blocking intracellular metabolism are being explored (32). Other phenomena which may play a role in the pathogenesis of viral infection are also being investigated. These include the production of toxins by viruses such as influenza, the production of states of hypersensitivity such as are reflected in the development of positive skin tests, and the phenomenon termed interference. Interference is the prevention or inhibition of multiplication of a virus caused by the presence in the animal of another virus. Interference may occur between viruses which differ completely in antigenic structure. These and many other problems remain to be studied before one can complete the story of the pathogenesis, or mode of production of viral infections.

REFERENCES

1. BURNET, F. M.: *Virus as Organism*. Harvard University Press, Cambridge, Mass. 1945.
2. ADAMS, F.: *The Genuine Works of Hippocrates*. William Woods and Co., New York, 1891.
3. HENLE, G., HENLE, W., WENDELL, K. K., AND ROSENBERG, P.: Isolation of Mumps Virus from Human Beings with Induced Apparent or Inapparent Infections. *J. Exp. Med.*, 88: 223, 1948.
4. KILHAM, L.: Mumps Meningoencephalitis with and without Parotitis. *Am. J. Dis. Child.*, 78: 324, 1949.
5. FLORMAN, A. L., AND KUTCH, J. H.: Specific Serological Reactions which follow naturally acquired Mumps. *J. Immunol.*, 63: 281, 1949.
6. FLORMAN, A. L., FISCHER, A. E., AND MOLOSHOK, R. E.: Evaluation of the Mumps Skin Test. *Pediatrics*, 5: 469, 1950.
7. FLORMAN, A. L., SCHICK, B., AND SCALETTAR, H. E.: Placental Transmission of Mumps and Streptococcus MG Antibodies. *Proc. Soc. Exp. Biol. and Med.*, 78: 126, 1951.
8. FLORMAN, A. L., AND KARELITZ, S.: The Fate of Mumps Antibodies following their passage through the Placenta. *J. Immunol.*, 71: 55, 1953.
9. HENLE, G., BASHE, W. J., JR., BURGOON, C. F., HUNT, G. R., JR., AND HENLE, W.: Studies on the Prevention of Mumps. III. The Effect of Subcutaneous Injection of Inactivated Mumps Virus Vaccines. *J. Immunol.*, 66: 561, 1951.
10. Committee on Typing of the National Foundation for Infantile Paralysis: Immunologic Classification of Poliomyelitis Viruses: Discussion of Results and General Summary. *Am. J. Hyg.*, 54: 191, 1951.
11. BODIAN, D. A.: Reconsideration of the Pathogenesis of Poliomyelitis. *Am. J. Hyg.*, 55: 414, 1952.
12. HORSTMANN, D. M.: Poliomyelitis Virus in Blood of Orally Infected Monkeys and Chimpanzees. *Proc. Soc. Exper. Biol. and Med.*, 79: 417, 1952.
13. BODIAN, D.: Pathogenesis and Immunity in Poliomyelitis. *Pediatric Clinics of North America*, 1: 5, 1953.
14. HAMMON, W. McD., CORIELL, L. L., AND WEHRLE, P. F.: Evaluation of Red Cross Gamma Globulin as a Prophylactic Agent for Poliomyelitis. IV. Final Report of Results Based on Clinical Diagnosis. *J. A. M. A.*, 151: 1272, 1953.
15. NATIONAL RESEARCH COUNCIL: The Distribution and Use of Gamma Globulin. *Pediatric Clinics of North America*, 1: 52, 1953.
16. SALK, J.: Studies in Human Subjects on Active Immunization Against Poliomyelitis. *J. A. M. A.*, 151: 1081, 1953.
17. KOPROWSKI, H., JERVIS, G. A., AND NORTON, T. W.: Immune Responses in Human Volunteers Upon Oral Administration of a Rodent Adapted Strain of Poliomyelitis. *Am. J. Hyg.*, 55: 108, 1952.

18. VAN ROOYEN, C. E., AND RHODES, A. J.: *Virus Diseases of Man*. Chap. XX. T. Nelson and Sons, N. Y. 1948.
19. SCOTT, T. F. MCN.: *Diseases Caused by the Virus of Herpes Simplex in Viral and Rickettsial Infections of Man*. Edited by Rivers, T. M., J. B. Lippincott Co., Phil., Second Ed., 1952.
20. ZUELZER, W. W., AND STULBERG, C. S.: Herpes Simplex Virus as the Cause of Fulminating Visceral Disease and Hepatitis in Infancy. *Am. J. Dis. Child.*, 83: 421, 1952.
21. FLORMAN, A. L., AND MINDLIN, R. L.: Generalized Herpes Simplex in an Eleven-Day-Old Premature Infant. *Am. J. Dis. Child.*, 83: 481, 1952.
22. BUDDINGH, G. J., SCHRUM, D. I., LANIER, J. C., AND GUIDRY, D. J.: Studies of the Natural History of Herpes Simplex Infections. *Pediatrics*, 11: 595, 1953.
23. GAJDUSEK, D. C., ROBBINS, M. L., AND ROBBINS, F. C.: Diagnosis of Herpes Simplex Infections by Means of Complement Fixation Test. *J. A. M. A.*, 149: 235, 1952.
24. NAGLER, F. P. O.: A Herpes Skin Test Reagent from Amniotic Fluid. *Australian J. Exp. Biol. and Med. Sci.*, 24: 103, 1946.
25. MEYER, K. F., AND EDDIE, B.: A Review of Psittacosis for the Years 1948-1950. *Bull. Hyg.*, 26: 1, 1951.
26. FRANCIS, T., JR., QUILLIGAN, J. J., JR., AND MINUSE, E.: Identification of Another Epidemic Respiratory Disease. *Science*, 112: 495, 1950.
27. FRANCIS, T., JR.: Factors Conditioning Resistance to Epidemic Influenza. *Harvey Lectures*, 37: 69, 1941-1942.
28. SALK, J.: Use of Adjuvants in Studies on Influenzal Immunization. *J. A. M. A.*, 151: 1169, 1953.
29. MACLEOD, C. M.: Relation of the Incubation Period and the Secondary Immune Response to Lasting Immunity to Infectious Diseases. *J. Immunol.*, 70: 421, 1953.
30. BAWDEN, F. C.: Virus and Its Interaction with the Host Cell: Biochemical Aspects, in Poliomyelitis, Papers and Discussions Presented at the Second International Poliomyelitis Conference. J. B. Lippincott Co., Phil., 1952.
31. FLORMAN, A. L.: Viral Hemagglutination, A Review and Some Observations. *J. Mt. Sinai Hosp.*, 18: 286, 1952.
32. HORSEFALL, F. L., JR.: External Factors Influencing Virus, in Poliomyelitis, Papers and Discussions Presented at the Second International Poliomyelitis Conference. J. B. Lippincott Co., Phil., 1952.

LOCALIZED HYPERTROPHIED GASTRIC FOLDS: DIFFERENTIATION FROM CARCINOMA OF THE STOMACH¹

STUART I. GURMAN,² M.D. AND BERNARD S. WOLF, M.D.

Recent literature has contained numerous references to hypertrophied gastric folds and the similarity of the roentgen appearance to carcinoma of the stomach (1, 2, 3, 4). The attempt to distinguish between the two conditions has been delayed due to the prevalence of a belief, fostered by Konjetzny and others, (3, 5) that gastritis was a precursor to carcinoma and should be treated in similar fashion. This view is no longer generally accepted (6, 7). The attempt therefore to differentiate carcinoma of the stomach from localized fold hypertrophy, with or without adenomatous change is worthy of investigation (8, 9, 10).

The diagnostic problem for both the roentgenologist and the gastroscopist is not as difficult when the entire stomach shows enlarged folds (11, 12, 13). When, however, the abnormality is confined to a localized area in the stomach, differential diagnosis may be extremely difficult (14, 15).

We have had such difficulties in a group of six cases, in which the x-ray examination revealed a localized filling defect, suggesting a mass in the stomach. In two of these, the diagnosis of carcinoma was made and the patients were operated upon. In the remaining four cases, the possibility that the observed defect was due to enlarged folds was strongly suggested. Of this latter group, two were operated upon with confirmation of the diagnosis and the remaining two have been observed over a period of years with no change in their status.

A review of these cases revealed certain helpful characteristics that may serve to differentiate hypertrophied folds from carcinoma.

CASE REPORTS

Case 1. (Adm. 617747) Mr. C. R., aged 65, was admitted with the chief complaint of rectal bleeding of eight years duration. During the previous year the patient had noted a six pound weight loss. Sigmoidoscopy and barium enema were negative. Barium meal examination revealed a filling defect with an irregularity of the mucosa in the area of the antrum (fig. 1). The patient was then gastroscopied. A coarsely nodular mucosa with a necrotic surface was described, suggesting an infiltrating carcinoma. Since this confirmed the impression of the Radiology Department, on 11/2/50, a subtotal gastrectomy was performed. The specimen revealed 6-7 irregularly defined areas of nodular mucosal thickening, extending into the lumen and fading off into normal mucosa. Microscopically, these represented localized areas of adenomatous hyperplasia.

A review of the roentgenograms (fig. 1) reveals the filling defect in the antrum. However, mucosal folds are noted to extend through the "mass". Pressure studies of this area reveals a peculiar stellate collection of barium at the termination of one of these folds along the greater curvature (fig. 2).

A diagrammatic illustration of the resected stomach shows the localized collection of

¹ From the Department of Radiology, The Mount Sinai Hospital, N. Y., N. Y.

² National Cancer Institute Fellow in Radiology.



FIG. 1. Case 1. Filling defect on greater curvature aspect of stomach. Linear streaks extend into the filling defect.



FIG. 2. Case 1. Pressure studies. The large folds are accentuated. Pockets of barium with angular contours are seen between the folds along the contour of the stomach.

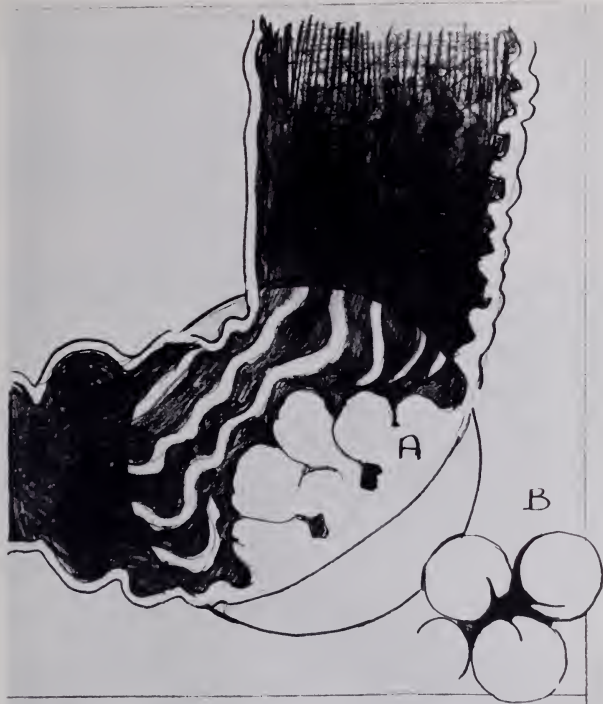


FIG. 3. Diagrammatic illustration of folds in resected stomach in Case 1. Circle indicates effect of compression. The "filling defect" is composed of large, tortuous folds with intervening linear "valleys". Insert (B) indicates mechanism of formation of the angular or stellate pockets of trapped barium.

the thickened polypoid folds (fig. 3). When pressure is applied during a roentgen study in the encircled area, the anterior and posterior walls of the stomach are brought into apposition, separated only by the enlarged folds and the barium trapped among them. The appearance of the residual barium seen on the films can be explained in the following fashion. The filling defects are due to individual larger folds rather than a single mass. The stellate or geometrically angular collections of barium are the result of the configuration of the available space between the rounded polypoid defects (B). Since the filling defect is rugal in nature, barium between the folds may be seen to extend to the contour of the stomach through the apparent mass.

Case 2. (Adm. 623273) Mr. J. S., aged 43, was admitted because of persistent anemia.



FIG. 4. Case 2. Demonstrates the filling defect and the streaks and pockets of barium within the defect.



FIG. 5. Case 3. Filling defect on lesser curvature aspect of stomach. Barium streaks are seen within the defect as well as around the periphery of the lesion along the contour of the stomach.



FIG. 6. Case 4. Polypoid folds demonstrated by streaks and pockets of barium in the interstices. The appearance is variable, depending on the amount of pressure applied and the degree of filling with barium.

Patient had been followed at another hospital for episodes of hematemesis and epigastric pain. Gastro-intestinal examinations there revealed a lesion in the stomach that was interpreted as probably a gastric tumor. An exploratory gastrotomy was carried out and no tumor was found. A liver biopsy done at the same time, showed portal cirrhosis. The patient's symptoms of epigastric pain continued. Because of this and the persistence of guaiac positive stools and anemia, the patient was admitted to this hospital. A barium meal examination revealed a constant filling defect in the antrum (fig. 4). This was larger than on the previous examination. No varices were demonstrated. The patient was explored a second time and a subtotal gastric resection performed. The specimen showed a localized collection of thickened rugal folds with hyperplastic gastric mucosa. Review of the films (fig. 4) again revealed an angular collection of barium at the termination of a streak of barium extending through the "mass".

These two cases illustrate the appearance of hypertrophied folds on the greater curvature aspect of the stomach. The difficulty in the diagnosis was due to their occurrence in

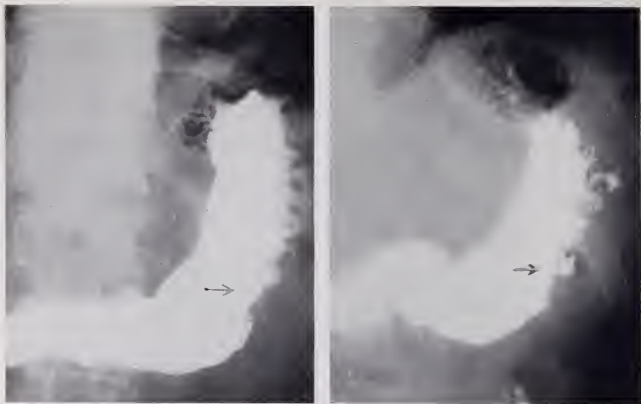


FIG. 7. Case 5. Circumscribed defect on the greater curvature. On the filled stomach, the localized nature of the changes is almost obscured despite the fact that the lesion is seen in profile. This indicates a degree of distensibility at the site of the lesion not characteristic of carcinoma. Individual large folds extend upward to the fundus.

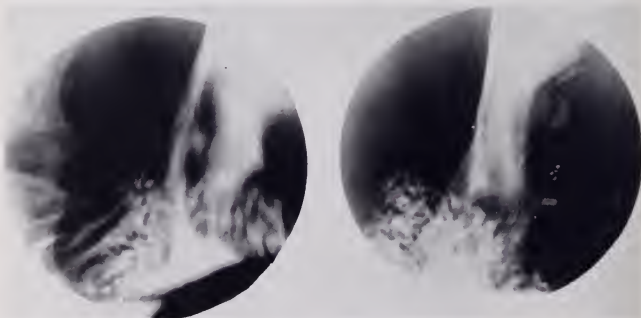


FIG. 8. Case 5. Pressure studies, "en face" view, barium within the defect has an angular margin. In the profile view, a pocket of barium extends to the stomach contour.

a localized packet. The presence of localized enlarged folds on the lesser curvature is considerably less common and the diagnosis of a benign condition in the presence of a filling defect in this region is rarely considered.

Case 3. Mr. R. T., a 72 year old male, with minimal complaints of extremely short duration, showed a filling defect on the lesser curvature aspect of the stomach (fig. 5). Because of the presence of fine streaks of barium extending through the filling defect and a streak of barium along the contour of the stomach surrounding the defect, a diagnosis of lo-



FIG. 9. Case 6. Defect on greater curvature with "deep" pocket extending to stomach contour.

calized fold hypertrophy with discrete polyps was suggested. A subtotal gastrectomy was performed. The specimen revealed two sessile polyps, approximately 1.5 cm. in diameter, in an area of thickened folds. Hyperplastic mucosa was seen microscopically.

Case 4. (Adm. 612478) Mrs. H. B., aged 57, gave a history of painless swelling of the abdomen of eight months duration and a three month history of anorexia and epigastric pain. A clinical diagnosis of portal cirrhosis was made. A barium meal examination showed an apparent polypoid mass in the antrum. The stomach in this area appeared to be quite rigid. A diagnosis of polypoid carcinoma of the stomach was suggested and despite the patient's general condition, a subtotal gastrectomy was performed. The specimen showed thickened, cobblestone mucosa with superficial ulcerations.

The roentgenograms in this case (fig. 6) demonstrate the "en face" appearance of the thickened folds. The enlarged folds, the thin streaks of barium coursing through the filling defect, the stellate collections of barium between the polypoid folds and the variable appearance depending on the amount of pressure applied or the degree of filling are well seen.

The following two patients have not been explored. They have been followed for two and three years with no change in their general condition or in the roentgenograms. The diagnosis of hypertrophied folds is based on the experience gained in the previous cases.

Case 5. Mr. G. R. was referred for a barium meal because of a history of epigastric pain. Examination revealed a filling defect on the greater curvature portion of the stomach

(fig. 7) which on pressure studies seemed on several films to be discrete (fig. 8). However, the presence of streaks and angular collections of barium within the defect and its variable appearance with different amounts of pressure suggested the possibility of a benign collection of thickened folds. This diagnosis has apparently been confirmed by the subsequent course.

The last patient, Case 6, with a short history of epigastric pain, weight loss and mild anorexia also showed an apparent defect on the greater curvature aspect of the stomach (fig. 9). A central "pocket" was present, however, which extended to the contour of the stomach and gave the impression of barium trapped between thick folds. Additional thin streaks of barium could be seen on other films within the apparent mass. Several follow-up studies have revealed no change in the appearance of the lesion.

DISCUSSION

The roentgen characteristics described above apply to filling defects produced by a localized group of large folds independent of etiology. The common cases of this appearance are: 1) adenomatous hyperplasia with or without discrete polypi and 2) inflammatory changes of a hyperplastic character with or without discrete pseudopolypi. Superficial ulceration may be present in both of these conditions. There is considerable controversy over the question as to whether these lesions are precancerous. Despite this uncertainty, the recognition of the benign nature of the lesion, at the time of observation at least, may often be clinically important. In elderly individuals or in individuals with some other lesion which makes operative intervention hazardous, the decision may be made to observe the lesion instead of performing immediate resection.

Occasionally, large folds with otherwise normal structure may be seen—"giant" folds. However, such folds rarely appear as a discrete pocket producing a localized filling defect. "Giant" folds may also be caused by lymphosarcoma. The recognition of mucosal destruction, abnormal hypotonicity of the stomach, clinical features suggesting the presence of a malignant lesion, and the rapid downhill course are usually sufficiently clear to make this diagnosis.

SUMMARY

Six cases with localized filling defects on barium meal examination due to hypertrophied folds have been presented. The defects have been on the lesser curvature, greater curvature and posterior wall of the stomach. A review of the roentgen findings revealed certain helpful characteristics that may serve to distinguish this condition from carcinoma.

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BIBLIOGRAPHY

1. TEMPLETON, F. E.: X-Ray Examination of the Stomach. Cleveland. The University of Chicago Press. 1944.
2. BOCKUS, H. L.: Gastro-Enterology. Philadelphia. W. B. Saunders Co. 1943.

3. KENNEDY, T. J.: Difficulties in the differential Diagnosis of Gastric Carcinoma and Gastritis. *Radiology*, 59: 367, 1952.
4. LYEL, D. and LEIDER, H. J.: Prepyloric Gastritis Simulating Gastric Carcinoma. *N. Y. State J. of Med.*, 50: 1483, 1950.
5. CURTIS, W. S.: Chronic Gastritis, A Review of the Literature. *Radiology*, 59: 317, 1952.
6. ANDERSON, W. A. D.: *Pathology*. St. Louis. C. K. Mosby, 1948.
7. GUISS, L. W., AND STEWART, F. W.: Distributions of Gastric Changes Accompanying Gastric Cancers in Various Locations. *Arch. Surgery*, 57: 624, 1948.
8. COLE, L. G., EWING, J. ET AL.: Symposium on Cancer of the Stomach. *Am. J. Surg.*, 31: 196, 1936.
9. INGERSOLL, C. F.: Speculations Concerning the Probable Evolution of Chronic Gastritis. *Radiology*, 59: 349, 1952.
10. GOLDEN, R.: *Diagnostic-Radiology*. New York. Thomas Nelson & Sons, 1936.
11. SHINDLER, R.: *Gastritis*. New York. Grune and Stratton, 1947.
12. BENEDICT, E. B.: Symposium on Gastric Neoplasms. Differential Diagnosis of Benign and Malignant Lesions of the Stomach by Means of the Flexible Operating Gastroscope. *Gastro-Enterology*, 14: 275, 1950.
13. MOERSCH, H. J.: Gastroscopic Differentiation of Gastritis from Carcinoma of the Stomach. *Gastro-Enterology*, 8: 284, 1947.
14. VAUGHAN, W. W.: Antral Gastritis: Roentgenologic and Gastroscopic Findings. *Radiology*, 44: 531, 1945.
15. BERG, H. M.: Antral Gastritis. *Radiology*, 59: 324, 1952.

ABSENCE OF RIGHT KIDNEY: RETROPERITONEAL (METANEPHROGENIC) CYST

GORDON D. OPPENHEIMER, M.D. AND JOSEPH M. SILAGY, M.D.

New York, N. Y.

INTRODUCTION

The human kidney goes through a complicated embryologic development, passing successively through the stages of pronephros, mesonephros and metanephros in the recapitulation of its evolution. Any disturbance in the harmonious progression of these stages results in failures of development or abnormalities (1). Of the multitude of anomalies of the genito-urinary tract that have been described, one interesting type is congenital, unilateral kidney absence associated with a homolateral retroperitoneal cystic mass. Only a few such cases have been reported in the literature (2, 3, 4). The present case is added because of the interesting clinical and embryologic considerations as well as the successful surgical treatment.

CASE HISTORY

The patient (H. P., #520976), a 4 year old white male, was admitted for the first time to the Mount Sinai Hospital in April 1944 because of epigastric and right lower quadrant pain and vomiting of six days' duration. There had been an antecedent upper respiratory infection and the child had been complaining for the preceding four months of recurrent abdominal discomfort. There had been attacks of constipation, vomiting and diarrhea lasting several days at a time. No urinary symptoms had been present. There was no history of familial diseases. The child had been delivered spontaneously at term and there were no birth complications. His development had been normal.

Physical examination showed a thin, poorly-nourished boy. Temperature was 101°. Positive findings included tenderness in the right lower quadrant of the abdomen. Moderate spasm was encountered over a large, round mass which was also palpable on the right side upon rectal examination. The scrotum and testicles were normal. The white blood count was 18,900 and the urine was normal.

A tentative diagnosis of appendiceal abscess was made, and an exploratory laparotomy was performed. A modified McBurney incision was made and, as the internal oblique muscle was split down to the transversalis fascia, a large, tense, cystic mass was encountered which was extra-peritoneal and displaced the spermatic cord laterally to a point just medial to the anterior superior iliac spine. The spermatic cord was severed during the dissection. The cyst was opened and evacuated of 500 cc. of clear, yellow fluid. The interior of the cyst was found to be smooth-walled and lobulated. It extended downward filling the pelvis, and upward along the right lumbar gutter. The edges of the cyst were marsupialized, and a portion of the cyst wall was excised for biopsy. This was subsequently reported as fibrous tissue. The postoperative course was complicated by secondary infection of the cyst and pneumonia.

Some days after the operation, urologic work-up was begun. The intravenous pyelogram showed a normal left kidney with good excretion of the contrast medium. No evidence of the presence of a right kidney could be made out.

Cystoscopic examination was performed under general anesthesia. The left half of the

* From the Urological Service, The Mount Sinai Hospital, New York, N. Y.



FIG. 1. Retrograde cystogram showing filling defect on right side of bladder produced by the extrinsic pressure of a retroperitoneal cyst.

inter-ureteric ridge was present and the left ureteral orifice, which was slightly dilated, was easily seen. The right half of the inter-ureteric ridge was absent. No ureteral orifice on this side could be made out. These findings were corroborated by subsequent examinations.

Patient was discharged to the Out-Patient Department, and at periodic intervals he was re-admitted and attempts were made to sclerose and obliterate the cyst by means of 50% glucose and, later, by 5% sodium morrhuate solutions. The drainage from the cyst gradually subsided. The wound was finally healed in 1945. The patient was followed for several years in the Out-Patient Department and while under observation, a fullness was noted to have developed in the right side of the abdomen. Other than a low grade fever, the patient was completely asymptomatic. He was re-admitted to the hospital in April of 1950 at the age of 10 years. There had been no urinary symptoms in the six years since he was initially observed.

Physical examination revealed a well developed and well nourished white male. Blood Pressure was 126/84. The heart and lungs were normal. There was a healed RLQ scar. The left testicle was normal, the right was atrophied. Combined recto-abdominal examination, under anesthesia, revealed a soft cystic mass approximating the size of a grapefruit which was palpable through the anterior and right lateral rectal wall.

Blood count was normal. Blood Urea Nitrogen was 12 mg. per 100 cc. Urine was normal.

The intravenous pyelogram showed the left kidney to be slightly larger than normal, but with no dilatation of the pelvis or calyces. The left ureter was normal. There was no evidence of a right kidney. A large filling defect was seen on the right lateral aspect of the bladder suggesting extrinsic pressure and this was confirmed by retrograde cystography (Fig. 1).

While under observation in the hospital, patient ran a low grade fever with daily elevations to 101° which were felt to be caused by infection in the retro-peritoneal cyst. It was therefore decided to extirpate the cyst.

OPERATIVE REPORT

On May 19, 1950, a modified Cherney incision was made which extended up the right side excising the old scar. The retroperitoneal area was exposed and a trilobulated retroperitoneal cyst was found. The lowermost, largest rounded portion occupied the right side of the pelvis and was imbedded in the wall of the bladder. It was enucleated from the bladder thereby requiring the bladder muscle to be sutured over the bulging mucosa and submucosa. A second portion of the cyst lying mesially over the sacrum and lower lumbar area was mobilized. Ascending from this portion was a long tubular structure, possibly narrowed by the previous sclerosing treatment. It extended upward to the right of the vena cava ending blindly in fatty areolar tissue beneath the diaphragm. No kidney or adrenal gland was seen. The cystic masses were completely extirpated. The cyst fluid was hazy and contained many pus cells.

PATHOLOGIC REPORT

"Dilated tubular structure, with several saccular dilatations; 26 cm. in length. At the upper end there are a few small tubules lined by cuboidal epithelium. Smooth muscle is present in the wall. No glomeruli seen in specimen submitted."

POSTOPERATIVE COURSE

The postoperative course was fairly smooth and the patient was discharged in good condition with the wound healed and firm. Follow-up examinations were performed every few months. When last seen, two years after the second operation, the patient was well. There were no urinary symptoms and the wound was well healed. No abdominal or rectal mass was palpable.

DISCUSSION

Unilateral absence of the kidney was known to the ancients; Aristotle stating that although an animal is never without a heart, yet it indeed may be found "without spleen, also with one kidney." However, one kidney may be lacking for a variety of reasons. One must distinguish carefully between agenesis, which denotes the failure of development; aplasia, in which only rudimentary renal tissue persists; atrophy, in which a normally formed kidney undergoes progressive destruction; and fusion, which occurs when the anlagen of the kidney on either side are joined into one. This discussion shall be concerned mainly with the first two categories.

The consensus of modern embryologic interpretation is that the complete development of the kidney is the result of the mutual influence and fusion of two healthy primordia. The actual excretory parenchyma arises independently in the mesoderm as the nephrogenic blastema. The anlage of the ureter begins as an out-pouching of the Wolffian duct just above its point of union with the primitive bladder. The ureteric bud grows into the nephrogenic blastema which subsequently finds its way up from the pelvis into the usual kidney site.

As the primitive bladder grows and differentiates, the terminations of the Wolffian ducts are carried caudally into the posterior urethra, and the ureters become incorporated and gain independent entrance into the bladder. The area bounded by the openings of the ureters and the openings of the Wolffian ducts becomes the trigone. The Wolffian ducts subsequently become part of the male genital system giving rise to the ejaculatory ducts, seminal vesicles, vasa deferentia and parts of the epididymes (5).

Defective germ plasma or failure of the two component anlagen of the kidney to meet the stress of physico-mechanical factors in the growing embryo will result in arrests and retardations in development, or anomalies.

It seems absolutely necessary that the ureteric bud get into the blastema in order to form a functional kidney, for the nephrogenic component does not differentiate normally in the absence of the ureteric component. Nonetheless, the former always appears as an anlage in spite of lesions that prevent the formation of the ureter.

Fortune (6) analyzed a series of cases of congenital one-sided kidney defect. In a group of 422 cases of renal agenesis verified by autopsy, the great majority was associated with congenital absence of the ureter (90% of cases in which ureter was mentioned). In 104 cases, the ureteral orifice was absent on the involved side with asymmetry of the trigone. Associated serious malformations of the genital tract were found in 128 of 183 females and 42 of 198 males.

The immediate cause of the unilateral kidney absence would appear to be the failure of the Wolffian duct to unite with the primitive bladder. Combinations of anomalies of both the renal and genital systems can thus readily be explained. Faulty growth of the Wolffian duct results in failure of development of the ureteric bud. This bud failing, the stimulus for normal kidney development is absent. Similarly, with improper growth of the Wolffian duct, those structures which in the male arise from it, must suffer.

The greater frequency of genital anomalies in the female is in consequence of the fact that the Muellerian duct is a later development than the Wolffian and thus has a greater chance of being involved in any lesion which operates to prevent normal renal and genital differentiation.

Experimental embryology confirms the description of kidney development noted above. Brown (7) analyzed the developing metanephros in a strain of mice whose kidneys had been rendered abnormal by means of irradiation. She found that where the ureteric bud did not penetrate into the nephrogenic blastema, no functional kidney developed. Arrested development of the Wolffian ducts appeared to be the primary cause of defective ureteral buds and thus of renal agenesis.

Boyden (8), working with chick embryos, noted that ureteral agenesis could be produced experimentally by interrupting the Wolffian duct in its zone of differentiation. Despite failure of the ureter to develop, the nephrogenic blastema did appear and assumed the form of the embryologic kidney, failing however, to differentiate into tubules and glomeruli. The ultimate fate of the blastema that formed in the absence of a ureteric bud could not be stated with certainty, but apparently, in the majority of cases, it was re-absorbed.

In the light of this discussion of normal, pathologic and experimental embryology, one may offer the following explanations of the clinical case which has been presented.

The first explanation postulates that for physico-mechanical or genetic reasons the ureteral bud on the right side failed to develop. In the absence of the inductive and organizing influence of the ureter, the nephrogenic blastema did not differentiate normally but underwent cystic degeneration, forming a metanephrogenic cyst. The presence of smooth muscle in the wall of the cyst is not easily explained by this analysis; it may have been derived from part of the bladder wall drawn out over the cyst.

A second explanation requires the supposition that normal development of the ureter and kidney took place with subsequent atresia of the lower end of the ureter and obstructive hydronephrotic atrophy. This view has little to commend it for no vestige of glomeruli or normal tubules could be found in the resected specimen, a finding most unlikely had any of these structures ever developed. The cystoscopic finding of an absent ureteral ridge and orifice on the affected side is additional evidence that the ureter did not actually ever develop, as Fortune (6), Nation (5), and Collins (10) state.

That the excised cystic mass represented a hugely dilated ureter with blind proximal and distal ends is a contention similarly open to the objection just cited; for the asymmetry of the trigone and the absent ureteral orifice on the involved side are strong evidence against it.

SUMMARY

A case of unilateral kidney absence with same sided retroperitoneal cyst has been presented. Marsupialization and attempts at sclerosing the cyst lining were ineffective and surgical extirpation was thereupon carried out with complete success.

The relevant normal, pathologic and experimental embryology have been reviewed in an effort to explain the abnormalities encountered in this unusual case.

BIBLIOGRAPHY

1. NICHOLSON, G. W.: The Kidneys and Development. *Guys Hospital Reports*, 77: 362, 1927.
2. KRAUSS, L. W. AND STRAUSS, R.: Retroperitoneal Cyst Arising in Persistent Metanephros with Congenital Absence of Right Kidney and Ureter. *J. Urol.*, 34: 97, 1935.
3. KORNBLUM, K. AND RITTER, J. A.: Retroperitoneal Cyst with Agenesis of Kidney. *Radiology*, 32: 416, 1939.
4. WEINGARTEN, F. F., OREM, JOHN M., AND COX, O. C.: Agenesis of the Right Kidney with Retroperitoneal Cyst Arising in a Persistent Metanephros. *J. Urol.*, 57: 829, 1947.
5. CHWALLA, RUDOLF: *Zeitschrift fur Anat. und Entwicklung*, 83: 615, 1927.
6. FORTUNE, C. H.: Significance of Congenital One-sided Kidney Defect. *Am. Int. Med.*, 1: 377, 1927.
7. BROWN, A.: Analysis of Developing Metanephros in Mouse Embryos with Abnormal Kidneys. *Am. J. Anat.*, 47: 117, 1931.
8. BOYDEN, E. A.: Congenital Absence of Kidney. *Anat. Record*, 52: 325, 1932.
9. NATION, E. F.: Renal Agenesis. *Surg., Gynec. and Obstet.*, 79: 175, 1944.
10. COLLINS, D. C.: Congenital Unilateral Agenesis. *Annals Amer. Surg.*, 95: 715, 1932.

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CONTENTS

THE STIMULUS FOR ERYTHROPOIESIS, <i>Walter S. Root, Ph.D.</i>	331
THE LIMITATIONS OF THE LABORATORY IN ANTIBIOTIC THERAPY. <i>Bernard M. Wagner, M.D.</i>	339
SHOULD THE PATIENT KNOW THE TRUTH? <i>Bernard C. Meyer, M.D.</i> .	344
THE DEVELOPMENT OF AN ACQUIRED PULMONARY CYST. <i>Henry J. Heimlich, M.D., F.A.C.S.</i>	351
THE CAPACIGRAPH, AN INSTRUMENT FOR RECORDING CARDIAC OUT- PUT. <i>Herbert Mann, M.D.</i>	360

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* Deceased

THE STIMULUS FOR ERYTHROPOIESIS^{1, 2}

WALTER S. ROOT, Ph.D.

New York, N. Y.

The values for the red cell count, hematocrit reading, and hemoglobin level found in normal men and women vary only slightly from individual to individual. Red cell volume or mass as measured by modern techniques, give figures which differ somewhat depending upon the method used (1). Nevertheless, a normal range of values is recognized. As is well-known, changes in the concentration and mass of the erythrocytes whether produced by external loss, as in hemorrhage, or by the introduction of foreign red cells soon disappear and the concentration and mass of red cells return over a period of days to previous levels. The relative constancy of red cells and hemoglobin has led to the assumption that under ordinary circumstances their rate of formation balances nicely their rate of destruction. Presumably the organism possesses some mechanism which regulates this balance. In the following discussion we shall be concerned only with the stimulus for erythropoiesis in an organism in nutritional balance.

BONE MARROW

For nearly a hundred years (2), it has been known that in adult mammals red blood cells are formed and mature in the red bone marrow. Extramedullary sites of erythropoiesis have been observed (3), but these are generally regarded as a compensatory response to certain conditions of stress. The actual volume of the bone marrow may be greater than is generally suspected, for Fairman and Whipple (4) find that it may amount to some 300 ml. in a 10 kgm. dog. Of this, one fifth or about 60 ml. may be red marrow. In a recent study Root, Allen and Gregersen (1) have determined simultaneously the red cell volume by the P^{32} and the carbon monoxide (CO) methods. The results show that CO measures a 12 per cent greater volume than does P^{32} . If a value of 2 per cent can be assigned to myoglobin as supposed by Root, Roughton and Gregersen (5), The volume of the red bone marrow in a 10 kgm. dog would amount to some 40 to 50 ml. Although repeated hemorrhages will produce an expansion of the erythroid marrow and increased rates of red cell and hemoglobin production, the volume of the red bone marrow is not necessarily an index of its ability to produce red cells and hemoglobin (6). Grant (7) has attempted to measure the erythroid activity by temporarily arresting mitosis with colchicine and counting the number of mitotic figures in marrow samples.

¹ Read as the first of the 1954 series, Seminars in Hematology, The Mount Sinai Hospital, January 20, 1954.

² From the Department of Physiology, College of Physicians and Surgeons, Columbia University, New York, N. Y.

Bone Marrow Hypoxia

Miescher (see 3) seems to have been the first to suggest that a relative degree of hypoxia is present in the bone marrow at all times, and that this constitutes a stimulus for erythropoiesis, ensuring a steady supply of red blood cells to replace those destroyed each day. At an altitude the oxygen tension and content of the arterial blood would be decreased, subjecting the bone marrow to a greater degree of hypoxia and, therefore, more intensely stimulating erythropoiesis. This explanation has been extended to other types of hypoxia (8) commonly associated with an increased rate of red cell production. Thus, anemic hypoxia, as in chronic hemorrhage, chronic carbon monoxide inhalation, and certain types of secondary anemia are presumed to stimulate the bone marrow because a low or defective oxygen capacity exists. Erythroid stimulation has been supposed to occur when the blood flow through the marrow is decreased by marked vasoconstriction of the marrow vessels, or by a thickening of the arteriolar walls. Also, it has been suggested that the high metabolic rates of myeloid or tumor cells may lower the oxygen tension in the vicinity of the erythroid elements, stimulating the latter. The evidence for hypoxic stimulation of bone marrow is indirect and rests upon the association of erythroid activity with conditions known to produce hypoxia.

The Oxygen in Bone Marrow Blood

In 1947 Grant and Root (9) measured the oxygen saturation and tension in the first 0.15 ml. of blood removed from the red marrow. The removal of 30 per cent of the blood volume of dogs over a period of 3 days did not produce any reduction in either the oxygen saturation or tension of the bone marrow blood. During the succeeding 3 weeks the lost red cells and hemoglobin were regenerated without evidence of the existence of marrow hypoxia. In a further study Grant (10) maintained dogs for 100 days at moderate and constant anemic levels by frequent small hemorrhages. Although as much as 3.2 grams of hemoglobin were formed each day by some of these animals, no significant difference was found in the oxygen saturation of bone marrow blood during the anemic period as compared with measurements made before bleeding. This work has been repeated upon man by Berk et al. (11), and by Schwartz and Stats (12) who compared the oxygen in the blood taken from the bone marrow of normal individuals with that obtained from patients suffering from anemia and polycythemia vera. More recently Hecht and Samuels (13) studied the oxygen in the bone marrow blood of a variety of patients. Their work indicates that hypoxia of the marrow is present in individuals in whom the arterial oxygen tension is reduced, or under conditions of slowed blood flow. However, erythropoiesis may be quite intense, as in polycythemia vera, in the absence of any defect in oxygenation of the bone marrow blood.

The validity of these studies depends upon whether or not a true sample of bone marrow blood was obtained. In this connection it can be said that the first 0.1 to 0.2 ml. of material obtained from the bone marrow closely resembles marrow histologically. Larger samples of 0.25 to 0.5 ml. appear to be diluted

from 40 to 100 per cent by peripheral blood (14). Presumably smaller samples would be less contaminated. At any rate the blood flowing through the red marrow must be at or near diffusion equilibrium with the growing erythroid cells within the sinusoids.

In Vitro Studies

Several investigators (see 3, 15) have shown that the relative growth rates of marrow samples in tissue culture are decreased at low oxygen tensions and increase when the oxygen pressures are raised. A study of the metabolic activity of isolated red marrow also fails to support the conception that erythroid stimulation is produced by lowered oxygen tension (16).

Experimental Production of Local Marrow Hypoxia

A number of attempts have been made to stimulate the erythropoietic activity by placing a tourniquet about a limb, by ligating the nutrient arteries of the long bones, or by injecting cyanide into the nutrient artery (see 3). In all of these investigations the hypoxia induced was of short duration and no convincing evidence of increased erythropoietic activity was obtained.

Summary

The association of conditions of chronic hypoxia with erythropoietic stimulation is well established. Indeed, exposure to lowered oxygen tensions is probably the method of choice for inducing increased activity of the red bone marrow. However, there is no convincing evidence that lowered oxygen tensions exert their effects directly upon the marrow tissue. Presumably hypoxia acts at some other site, the bone marrow being activated secondarily. The nervous system has been considered in this way particularly by European workers (see 3).

THE NERVOUS SYSTEM

Bone marrow is richly supplied with sympathetic and afferent nerve fibers (17). The latter carry impulses arising in receptors imbedded in the parenchyma of the marrow. The sympathetic nerve fibers innervate the smooth muscle of the blood vessels and are vaso-motor in function (see 3). Many of the reports found in the literature are concerned with the immediate effects of: cutting or stimulating the nerves supplying the bone marrow, the injection of vaso-constricting drugs, the administration of electric shocks, filling the cerebral ventricles with air, lumbar and cisternal punctures, the application of diathermy to the brain stem, and placing lesions in various parts of the nervous system (see 3). It seems doubtful that short-term experiments of this sort can supply information of value for an understanding of erythropoiesis. The mere appearance of a reticulocytosis, or even of an increase in the red cell count cannot be accepted as indicating any more than a washing out of cells already present in depots.

Of greater significance is the often cited study of Schafer (18) in which generalized vasospasm and hypertension were induced by removal of the carotid sinuses and section of the depressor components of the vagus nerves. Five of

13 dogs were reported to be polycythemic as estimated by the red cell volume (dye and hematocrit). Two of the polycythemic dogs were totally sympathectomized after which the red cell mass decreased and red cell counts, hemoglobin concentrations, and hematocrit readings returned to the control values. Recently, Sisson, Cain and Root (19) have repeated Schafer's experiments. The red cell volumes were measured with P^{32} and the plasma volumes were determined by means of the blue dye, T-1824. The volumes estimated immediately after the final operation and in some instances measured repeatedly over a period of 7 months did not differ significantly from the control values. The completeness of the operative procedures is indicated by the fact that all of the operated animals showed hypertension.

A number of experimental observations indicate that sympathetic innervation is not an essential factor in erythroid stimulation. Thus, Warren (see 3) found the same degree of erythroid hyperplasia in the marrow of denervated and control limbs when rabbits were exposed to lowered atmospheric pressure. Also, Orahovats and Root (20) have shown that totally sympathectomized dogs produce red cells and hemoglobin as rapidly as the normal animal during prolonged periods of frequent hemorrhage. Similar results were obtained by Grant and Root (21) who exposed normal and sympathectomized dogs to repeated, intermittent low barometric pressure.

A large number of clinical reports of the occurrence of polycythemia in association with various lesions of the central nervous system have appeared (see 3, 22). These are open to the criticism that the evidence advanced is based largely upon clinical data and in only a few instances have anatomical or pathological observations been made. The blood counts given as an indication of the presence of polycythemia are often at the level of the higher range of normal values, and are rarely accompanied by further evidence of erythropoietic stimulation such as reticulocyte counts, bone marrow examination, or an increase in red cell volume.

The hazard of drawing conclusions from concentration data alone (red cell counts, hematocrit readings, hemoglobin measurements) is apparent from the following considerations: In animals, as the dog and the cat, the spleen acts as a reservoir for the storage of red blood cells (23). Changes in the degree of relaxation or contraction of the spleen as a result of anesthesia, fear, exercise, etc., can produce large changes in the hematocrit values, the red cell count, and hemoglobin measurements even though the red cell mass may have remained unchanged. In man the changes produced by splenic contractions are small or absent (24). Nevertheless, changes in plasma volume, such as those produced by acute dehydration (25) can increase the concentration of the formed elements without altering the red cell mass. On the other hand, the red cell volume may be reduced greatly by skeletal muscle trauma without a proportional decrease in hemoconcentration (26). The importance of these observations in clinical conditions has been emphasized recently by Wilson and Boyle (27) who studied the peripheral blood levels of erythrocytes and hemoglobin, and measured the blood volumes in 62 human subjects. They find that in the so-called anemia of

neurasthenia, the red cell counts and the hemoglobin concentrations are below the accepted normal standards, but the red cell mass lies within normal limits. According to Wilson and Boyle, decrease in plasma volume alone has caused in some patients enough change in the peripheral blood findings to result in a diagnosis of polycythemia and treatment by phlebotomy. They point out that an anemia occurring in pregnancy can be evaluated only by studying the blood volume as well as the peripheral blood. The possible existence of a decreased plasma volume in polycythemia vera suggests also that peripheral blood measurements may be an erroneous index of the severity of the disease.

Summary

The inadequacy of concentration measurements as well as the absence of carefully controlled histological studies have led clinicians who have reviewed the literature to state that there is no conclusive evidence for the regulation of erythropoiesis by the central nervous system (see 3).

THE ENDOCRINE GLANDS

The removal of almost any endocrine gland results in an anemia which, however, usually amounts to only a reduction of 10 to 20 per cent in the formed elements. Injection of an extract of the gland, or of the hormone produced by the gland causes the anemia to disappear (see 3, 28).

The pituitary gland, however, is of particular interest, for after hypophysectomy the red cell volume of the rat is said to decrease to nearly one half of the control value (29). The anemia is apparently due to the absence of the anterior lobe of the hypophysis (30). Oral administration of fresh sheep anterior pituitary not only repaired the anemia of hypophysectomized rats, but also brought the circulating red cell volume to higher than normal levels (31). These results confirm the previous reports of Flaks and his co-workers (see 3).

Despite these observations hypophysectomy does not appear to cause any serious defect in the erythropoietic mechanism, for hypophysectomized and normal rats show the same hemopoietic response to a simulated altitude of 22,000 feet (32). Moreover, the administration of cobalt corrects the anemia of hypophysectomy. The increase in the red cell volume is of the same magnitude as that found in normal rats treated with cobalt (33).

HEMOPOIETINE

A number of other concepts of the stimulus for erythropoiesis have been advanced (see 3). Of these, perhaps the most important is that suggested by Carnot and Deflandre (34) in 1906. These investigators injected 9 ml. of plasma obtained from slightly anemic rabbits into normal rabbits and noted in the latter a small increase in the number of red cells in the peripheral blood. Carnot introduced the word hemopoietine to designate the unknown stimulating substance in the plasma. Unfortunately, plasma from severely anemic rabbits did not have any effect on the red cell count. Single injections of small amounts of plasma containing presumably small amounts of hemopoietine does not seem a pro-

cedure capable of yielding consistent results. Perhaps for this reason the repetition of Carnot's experiment has produced both positive and negative results (see 3).

Ingenious procedures for supplying hemopoietine continuously or in large amounts, have been devised to test the Carnot hypothesis. Thus, Reissmann (35) has used parabiotic rats, i.e. artificial Siamese twins. The animals were placed for several hours a day in a special breathing chamber in which one member of a pair breathed a gas mixture containing 8 to 10 per cent oxygen while the other breathed air. A polycythemic response was noted in both members during the several weeks of study. The free exchange of red blood cells as well as plasma between the members of a parabiotic pair is well-known. However, the fact that the erythroid elements increased in the bone marrow of both animals is assumed to mean that an agent capable of stimulating the red bone marrow was formed in the hypoxic rat and passed by way of the circulation to his partner. Grant (36) carried out a somewhat different experiment by placing lactating rats and mice in a low pressure chamber for six hours a day while their litters remained at sea level pressure. After 1 to 2 weeks the circulating red cell concentration and the total body hemoglobin of the babies nursed by the intermittently hypoxic mothers were greater than those of babies nursed by control mothers kept at sea level pressures. Erslev (37) has repeated Carnot's original experiments except that exceedingly large amounts of plasma from bled rabbits were used. A significant rise in the number of reticulocytes were seen. Rabbits receiving repeated injections of plasma from anemic rabbits showed increases in the red cell count and in the hematocrit values in the peripheral blood and in the per cent of nucleated red cells in the bone marrow. These results confirm a study previously carried out by Hodgson and his associates (38).

The nature and the site of the production of hemopoietine are unknown. According to recent report, the presence of oxygen diminishes the erythropoietic activity of plasma taken from anemic animals (39).

CONCLUSION

Hypoxia is one of the commonest conditions associated with erythropoiesis, and it is one of the most convenient means of experimentally producing erythroid stimulation. However, hypoxia does not act directly upon the bone marrow. No convincing evidence has been advanced to demonstrate that erythropoiesis is controlled by the nervous system, nor by the hormones of any single endocrine gland. Presumably the lack of oxygen at some unknown region in the organism activates processes which release an erythroid stimulating agent (hemopoietine).

REFERENCES

1. ROOT, W. S., ALLEN, T. H. AND GREGERSEN, M. I.: Simultaneous Determinations In Splenectomized Dogs Of Cell Volume With CO And P^{32} And Plasma Volume With T-1824. *Am. J. Physiol.*, 175: 233, 1953.
2. NEUMANN, E.: Ueber die Bedeutung des Knochenmarkes für die Blutbildung. *Centralbl. f. d. med. Wissensch.*, 6: 689, 1868.
3. GRANT, W. C. AND ROOT, W. S.: The Fundamental Stimulus For Erythropoiesis. *Physiol., Rev.*, 22: 449, 1952.

4. FAIRMAN, E. AND WHIPPLE, G. H.: Bone Marrow Volume In Adult Dogs. *Am. J. Physiol.*, 104: 352, 1933.
5. ROOT, W. S., ROUGHTON, F. J. W., AND GREGERSEN, M. I.: Simultaneous Determinations Of Blood Volume By CO And Dye (T-1824) Under Various Conditions. *Am. J. Physiol.*, 146: 739, 1946.
6. ROBSCHKEIT-ROBBINS, F. S.: Hemoglobin And Red Cell Production In Experimental Hemorrhagic Anemia. *Ann. N. Y. Acad. Sci.*, 48: 641, 1947.
7. GRANT, W. C.: Measurement Of Erythroid Mitotic Activity In Bone Marrow By The Use Of Colchicine. *Proc. Soc. Exp. Biol. and Med.*, 77: 537, 1951.
8. CASTLE, W. B.: Disorders of The Blood in W. A. Soderman, *Pathologic Physiology*, Philadelphia, Saunders, 1950.
9. GRANT, W. C. AND ROOT, W. S.: The Relation Of O_2 In Bone Marrow To Post-hemorrhage Erythropoiesis. *A. J. Physiol.*, 150: 618, 1947.
10. GRANT, W. C.: Oxygen Saturation In Bone Marrow And In Arterial And Venous Blood During Prolonged Hemorrhagic Erythropoiesis. *Am. J. Physiol.*, 153: 521, 1948.
11. BERK, L., BURCHENAL, J. H., WOOD, T., AND CASTLE, W. B.: Oxygen Saturation Of Sternal Marrow Blood With Specific Reference To Pathogenesis Of Polycythemia Vera. *Proc. Soc. Exp. Biol. and Med.*, 69: 316, 1948.
12. SCHWARTZ, B. M. AND STATS, D.: Oxygen Saturation Of Sternal Marrow Blood In Polycythemia Vera. *J. Clin. Invest.*, 28: 736, 1949.
13. HECHT, H. H. AND SAMUELS, A. J.: Observations On The Oxygen Content Of Sternal Bone Marrow With Reference To Polycythemic States. *Fed. Proc.*, 11: 68, 1952.
14. BERLIN, N. I., HENNESSY, T. G., AND GARTLAND, J.: Sternal Marrow Punctures: The Dilution With Peripheral Blood As Determined By P^{32} Labelled Red Blood Cells. *J. Lab. and Clin. Med.*, 36: 23, 1950.
15. ASTALDI, G., BERNARDELLI, E., AND REBAUDO, G.: Research On The Proliferation Activity Of Erythroblasts At Low Atmospheric Pressure. *Experientia*, 8: 117, 1952.
16. WARREN, C. O.: Tissue Metabolism Studies On Bone Marrow. *Trans. N. Y. Acad. Sci., Ser. II*, 8: 222, 1945.
17. KUNTZ, A. AND RICHINS, C. A.: Innervation Of The Bone Marrow. *J. Comp. Neurol.*, 83: 213, 1945.
18. SCHAFER, P. W.: The Etiology And Treatment Of Polycythemia Rubra Vera. *Ann. Surg.*, 122: 1098, 1945.
19. SISSON, G., CAIN, A., AND ROOT, W. S.: The Effect Of Sectioning The Buffer Nerves On The Red Cell Volumes Of Dogs. *Fed. Proc.* in press.
20. ORAHOVATS, P. D. AND ROOT, W. S.: Effect Of Total Sympathectomy On Red Cell And Hemoglobin Production In The Chronically Anemic Dog. *Am. J. Physiol.*, 173: 324, 1953.
21. GRANT, W. C. AND ROOT, W. S.: Polycythemic Response Of Sympathectomized Dogs To Discontinuous Anoxia. *Am. J. Physiol.*, 173: 321, 1953.
22. HOLMES, C. R., KREDEL, F. F., AND HANNA, C. B.: Polycythemia Secondary To Brain Tumor. *South. Med. J.* 45: 967, 1952.
23. BARCROFT, J.: *Features In The Architecture Of Physiological Function*. Cambridge Univ. Press, 1934.
24. TAYLOR, R. D. AND PAGE, I. H.: Mechanism Of Erythemia. *Arch. Surg.*, 47: 59, 1943.
25. ELMAN, R.: *Parenteral Alimentation In Surgery*. Hoeber, New York, 1947, p. 56.
26. NOBLE, R. P. AND GREGERSEN, M. I.: Blood Volume In Clinical Shock. II. The Extent And Cause Of Blood Volume Reduction In Traumatic, Hemorrhagic And Burn Shock. *J. Clin. Invest.*, 25: 172, 1946.
27. WILSON, S. J. AND BOYLE, P.: Erroneous Anemia And Polycythemia; A Comparative Study Of Peripheral Blood And Blood Volume. *Arch. Int. Med.*, 90: 602, 1952.
28. ASCHKENASY, A.: Maladies Des Globules Rouges Et Desordres Endocriniens; Le Role Des Glandes Endocrines Dans L'erythropoiese. *Le Sang*, 23: 89, 1952.
29. BERLIN, N. I., VAN DYKE, D. C., SIRI, W. E., AND WILLIAMS, C. P.: The Effect Of

- Hypophysectomy On The Total Circulating Red Cell Volume Of The Rat. *Endocrinology*, 47: 429, 1950.
30. VAN DYKE, D. C., GARCIA, J. F., SIMPSON, M. E., HUFF, R. L., CONTOPOULOS, A. N., AND EVANS, H. M.: Maintenance Of Circulating Red Cell Volume In Rats After Removal Of The Posterior And Intermediate Lobes Of The Pituitary. *Blood*, 7: 1017, 1952.
 31. CONTOPOULOS, A. N., VAN DYKE, D. C., SIMPSON, M. E., GARCIA, J. F., HUFF, R. L., WILLIAMS, B. S., AND EVANS, H. M.: Increase In Circulating Red Cell Volume After Oral Administration Of Pituitary Lobe. *Blood*, 8: 131, 1953.
 32. FEIGIN, W. M. AND GORDON, A. S.: Influence Of Hypophysectomy On The Hemopoietic Response Of Rats To Lowered Barometric Pressures. *Endocrinology*, 47: 364, 1950.
 33. GARCIA, J. F., VAN DYKE, D. C., AND BERLIN, N. I.: Correction Of Anemia Following Hypophysectomy By Administration Of Cobalt. *Proc. Soc. Exp. Biol. and Med.*, 80: 472, 1952.
 34. CARNOT, P. AND DEFLANDRE, C.: Sur L'activite Hemopoietique Du Serum. *Compt. rend. Acad. d. se.*, 143: 384, 1906.
 35. REISSMANN, K. R.: Studies On The Mechanism Of Erythropoietic Stimulation In Parahibiotic Rats During Hypoxia. *Blood*, 5: 372, 1950.
 36. GRANT, W. C.: Influence Of Anoxia Of A Lactating Rat On The Blood Of Normal Baby Rats. *Am. J. Physiol.*, 171: 728, 1952.
 37. ERSLEV, A.: Humoral Regulation Of Red Cell Production. *Blood*, 8: 349, 1953.
 38. TOHA, J., HODGSON, G., AND WEASSON, E.: Efecto Eritropoyetico De Unjecciones Repetidas De Plasma De Conejos Anemizados Por Sangria En Conejos Normales. *Bol. de la Soc. de Biol. (Concepcion, Chile)* 27: 69, 1952.
 39. GUNTHER, B., HUDGSON, G., TOHA, J., AND QUAPPE, O.: The Inactivation By Oxygen Of The Erythropoietic Effect Of Plasma Of Rabbits Rendered Anemic By Bleeding. *Acta Physiol. Lat.-Amer.*, 1: 271, 1951.

THE LIMITATIONS OF THE LABORATORY IN ANTIBIOTIC THERAPY^{1, 2}

BERNARD M. WAGNER, M.D.³

New York, New York

The busy physician engaged in the general practice of medicine has successfully demonstrated his ability to use the available antibiotics. Most of the acute infectious processes encountered are readily controlled on dosage schedules recommended by the manufacturer. Practically, it is not necessary to identify the infecting agent or its susceptibility to antibiotics. In these instances, the practitioner depends primarily on his previous "antibiotic experience". Consultation with the laboratory is usually only when (a) the patient is hospitalized, (b) the site and nature of infection remain obscure, (c) single or combination antibiotic therapy has failed and (d) the process becomes chronic.

In addition to the determination of bacterial susceptibility to antibiotics, the laboratory can assist in the selection of antibiotic combinations, be on the alert for changing sensitivities and the development of cross resistance, and assay various body fluids for antibiotics when indicated. Also, the laboratory can promptly report the development of a superimposed infection arising as a complication of therapy.

The purpose of this paper is to briefly discuss a few procedures which have been of most value in the ultimate cure of the patient. These tests have been standardized and in operation for several years with the accumulation of data based on thousands of determinations. Emphasis is placed on the limits of interpretation in view of current knowledge.

BACTERIAL SUSCEPTIBILITY TO ANTIBIOTICS

There are at present two main types of tests: agar diffusion and tube dilution. Much has been said as to the individual merits of these procedures. Nevertheless, one fundamental fact has emerged, namely, that all susceptibility tests are qualitative and serve to differentiate between the susceptible and resistant organisms (1). Determinations of bacterial susceptibility to antibiotics yield relative and not absolute values. Except for certain exceptional clinical conditions, attempts to secure quantitative finite results are of little significance to the clinician.

The accuracy of the serial tube dilution procedure is proportional to the exactness of technique used. This procedure is too cumbersome for most busy routine bacteriology laboratories. The disc method (agar diffusion) is an easily performed test capable of yielding significant information quickly. Parallel

¹ From the Department of Pathology, The Mount Sinai Hospital, New York, N. Y.

² Read in part before the American Public Health Assoc., Nov., 1953.

³ Research Assistant, Department of Pathology, The Mount Sinai Hospital. (Formerly Chief, Infectious Disease Section, Laboratory Service, Walter Reed Army Hospital, Washington, D. C.)

TABLE I
Criteria for interpretation of susceptibility by a disc technique

ANTIBIOTIC	DOSAGE SCHEDULE	AV. MAX. BLOOD LEVEL	APPROXIMATE DOSE/DISC	REL. SUSCEPTIBILITY ZONE	
				Pres.	Abs.
Penicillin	300,000 u (Pro- caine) daily/ 100,000 u cryst. q. 3 hrs.	0.75-1.0 u/cc	1.0 u	1 u or less S	>1 u R
Streptomycin	0.5 gm. b.i.d.	15 meg/cc	15 meg	15 meg or less S	>15 meg R
Chloramphenicol	0.5 gm. q. 6 hrs.	15 meg/cc	15 meg	15 meg or less S	>15 meg R
Aureomycin	0.5 gm. q. 6 hrs.	4 meg/cc	4 meg	4 meg or less S	>4 meg R
Terramycin	0.5 gm. q. 6 hrs.	6 meg	6 meg	6 meg or less S	>6 meg R

S Susceptible, R Resistant.

From Einsenberg, G. M. and Wagner, B. M., *Am. J. Med. Sci.*, 223: 600, 1952.

studies by the disc and tube techniques have revealed excellent correlation at levels considered sensitive and resistant (2). The intermediate range, often referred to as "moderatively sensitive", gives inconstant disc results when compared to the tube values. While values obtained from the tube dilution may characterize the sensitivity of the particular bacterial strain, this intermediate range is not easily translated into terms of dosage. Since the disc method is based on average blood levels achieved with recognized dosage schedules, the clinical value of the disc result is equal to the tube method. Thus, the disc test is a rapid, effective procedure designed for the clinician, while the tube method is used in special cases and for laboratory research. Incidentally, claims that the tube dilution procedure can give information as to the mechanism of action of the antibiotic tested are not founded in fact (Table I).

The zone of suppressed bacterial growth surrounding a disc is with certain limitations a measure of the relative susceptibility of the organism (3). After incubation, if a clear zone is present around a disc containing an amount of antibiotic equal to the average maximum blood level produced by routine therapy, the organism is considered sensitive. Absence of an inhibitory zone labels the organism resistant. The lag phase of the particular bacterial species must be considered as a limiting factor. Commercial paper discs (Difco) are reliable and some workers use more than one concentration for each antibiotic in an attempt to estimate the sensitivity range of the particular organism (4). Originally, we used our own discs (wet method). Good results have been obtained with the commercial products (dry method) so that the only wet disc employed

is for aureomycin. Our studies indicate that the commercial discs contain a huge excess of aureomycin in terms of clinical dosage and thus may give false sensitive values. Methods for preparation of wet discs have been previously published (2).

Cases of subacute bacterial endocarditis, bacterial meningitis, septicemia and urinary tract infections are clinical exceptions (5, 6). Organisms isolated from these serious disease processes are tested by a combined tube dilution-pour plate method (1). This is done in an effort to indicate at what antibiotic concentration growth is inhibited and is relatively irreversible. Body fluid assay for individual antibiotics becomes an important procedure in the therapy of these patients.

Patients receiving multiple antibiotics in cases of subacute bacterial endocarditis, have their sera tested by the method of Milzer (7) to determine the antibacterial activity of the sera in a gross manner against the previously isolated infecting agent. This gives the clinician a broad estimate as to the effectiveness of the therapeutic program. Our experiences confirm the reports of others in the effectiveness of penicillin and streptomycin in cases of enterococcal endocarditis regardless of laboratory sensitivity results.

Urinary tract infections often respond to individual antibiotics which have been considered ineffective based on sensitivity studies alone. This is no surprise to the clinician who realizes that the urine concentration of active antibiotic may far exceed the blood concentration and thus achieve levels not measured *in vitro*. Studies on non-specific urethritis (8) have demonstrated the striking lack of correlation between organisms isolated, antibiotic sensitivity and response to therapy. This is probably due to the isolation of secondary invaders while the etiologic agent remains unknown (9). Paraplegics with chronic urinary tract infections frequently show a changing bacterial flora while specific antibiotics are administered and in most instances a highly resistant *Proteus* or *Pseudomonas* species finally persists (6).

Thus, infectious processes which are difficult to reach are clinically resistant despite laboratory tests indicating susceptibility to antibiotics. Conversely, certain individual pharmacologic properties of the antibiotics produce concentration in certain organs and body fluids with levels of drug up to 25 times the circulating blood level. In such cases, clinical cures are achieved in the face of laboratory reported antibiotic resistant organisms. If these facts are kept in mind, then the method employing the average maximum blood concentration for use on a disc does not give conflicting information (10).

ANTIBIOTIC SYNERGISM AND ANTAGONISM

In vitro studies have demonstrated that certain antibiotics in combination may be antagonistic. An antagonistic effect of chloramphenicol, aureomycin and oxytetracycline on the bactericidal action of penicillin has been shown against certain penicillin-sensitive organisms (11, 12, 13). These experiments have been confirmed by us and others but the results are of variable clinical significance. One must remember that the aim of antibiotic therapy is to produce

TABLE II
Determination of antibiotic synergy
 Organism: Staph. aureus (coag. pos.) Source: Infected wound

Disc Tube M.I.C.	SENSITIVITY					
	Pen.	Strep.	Aureo.	Chloro.	Terra.	
	R 5 u	R 20	R 40	R 20	R 40	
	1% M.I.C.					
	100	50	40	30	20	10
	Pen Strep	5 20	2.5 10	2 8	1.5 6	1 4
Pen Chlor	5 20	2.5 10.	2 8	1.5 6	1 4	0.5 2

(No synergy between penicillin and streptomycin; definite synergy between penicillin and chloramphenicol.)

effective levels of the drug at the site of infection. Almost always, this means multiple dose therapy (14) and in addition the patient usually receives medical and surgical supportive treatment. The prevalence of this type of therapeutic regimen has failed to produce a single, unquestioned case of antibiotic antagonism in our studies.

Antibiotic synergy does occur and is of considerable value. A simple cleareut method to demonstrate synergy is used (13). Briefly, it entails the determination of the minimal inhibitory concentration (MIC) for each antibiotic of the combination against the infecting microorganism by a standard serial tube dilution method. Then a second tube dilution based on decreasing amounts of each MIC is set up and after the inoculum is added, each tube has a final volume of 1.0 ml. After overnight incubation, the tests are read and unless 40% or less of the original MIC of each antibiotic produces complete inhibition, there is no synergy. This does not necessarily negate the use of the combination in question, for certain clinical experiences go beyond the laboratory as indicated above. Thus, a report indicating antibiotic synergy is of therapeutic significance, while a negative result requires additional clinical interpretation (Table II).

Space does not permit discussion of the other laboratory functions in antibiotic therapy. Brief mention should be made of the importance of maintaining adequate records with cross indices of the data obtained. This statistical information is the foundation for the "antibiotic experience" of the laboratory. Such experience is invaluable in laboratory work aimed at helping the physician in the ultimate cure of the patient (15, 16).

SUMMARY

The antibiotic laboratory is largely a product of the clinician's need for guidance in therapy. Tests are designed to yield significant information as quickly

as possible. The limits of interpretation are not rigid and experience is necessary to evaluate the patient-laboratory findings. The main role of the laboratory is to suggest a logical course of therapy with careful follow-up studies. While the tests discussed have well recognized shortcomings, they serve the clinician as a rational guide to therapy.

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BIBLIOGRAPHY

1. EISENBERG, G. M.: Bacterial Susceptibility to Antibiotics I. Concept of Bacterial Inhibition. *J. Phila. Gen. Hosp.*, 2: 127, 1951.
2. WAGNER, B. M.: Rapid Determination of Bacterial Susceptibility to Antibiotics. *J. Phila. Gen. Hosp.*, 1: 16, 1950.
3. EISENBERG, G. M. AND WAGNER, B. M.: Bacterial Susceptibility to Antibiotics II. Determination by means of a Standardized, Routine Procedure having Clinical Significance. *Am. J. Med. Sci.*, 223: 600, 1952.
4. LIND, H. E.: The Rationale of Routine Antibiotic Sensitivity Determinations. *Antib. & Chemo.*, 3: 672, 1953.
5. WAGNER, B. M.: Penicillin Therapy in Subacute Bacterial Endocarditis. *Am. J. Med. Sci.*, 215: 84, 1948.
6. EISENBERG, G. M., ALEXANDER, J. D., JR., AND FLIPPIN, H. F.: Combined Antibiotic Therapy in Refractory Urinary Tract Infections. *J.A.M.A.*, 152: 1302, 1953.
7. SCHLICHTER, J. G., MACLEAN, H. AND MILZER, A.: Effective Penicillin Therapy in Subacute Bacterial Endocarditis and other Chronic Infections. *Am. J. Med. Sci.*, 217: 600, 1949.
8. WAGNER, B. M., MORSE, W. H. AND KUHN, D. M.: Recent Studies on Non-Specific Urethritis. *Am. J. Pub. Health*, 43: 853, 1953.
9. WAGNER, B. M. AND KUHN, D. M.: The Role of the Pleuropneumonia-like Organisms in Non-Specific Urethritis. *Bact. Proc. (abst.)*, 1953.
10. BROOM, N. H., MARTINEAU, P. C. AND YOUNG, D. C.: A Correlation of the Disk Antibiotic Sensitivity Tests and the Clinical Course of 69 Patients with Acute Bacterial Meningitis. *Antib. & Chemo.*, 3: 409, 1953.
11. JAWETZ, H. E. AND GUNNISON, J. B.: An Experimental Basis of Combined Antibiotic Action. *J.A.M.A.*, 150: 693, 1952.
12. JACKSON, G. G., LEPPER, M. H., SETO, J. AND DOWLING, H. F.: Antagonism and Addition from Combined Aureomycin and Penicillin in the Treatment of Pneumococcal Infections in Mice. *Am. J. Med. Sci.*, 225: 525, 1953.
13. ROMANSKY, M. J., FUSILLO, M. H., CALDWELL, E. AND ROBIN, E. D.: The Synergistic Action and Potential Applications of Antibiotic Combinations. *Med. Clin. N. Am.*, 35: 1, 1951.
14. EAGLE, H.: Speculations as to the Therapeutic Significance of the Penicillin Blood Level. *Ann. Int. Med.*, 28: 260, 1948.
15. FUSILLO, M. H. AND ROMANSKY, M. J.: The Simultaneous Increase in Resistance of Bacteria to Aureomycin and Terramycin upon Exposure to either Antibiotic. *Antib. & Chemo.*, 1: 107, 1951.
16. WAGNER, B. M., KUHN, D. M. AND FUSILLO, M. H.: Laboratory Studies of the Isonicotinic Acid Hydrazides in Tuberculosis. *U. S. Armed Forces Med. J.*, 3: 1741, 1952.

SHOULD THE PATIENT KNOW THE TRUTH?

BERNARD C. MEYER, M.D.¹

*"And oftentimes to win us to our harm
The instruments of darkness tell us truths,
Win us with honest trifles to betray us
In deepest consequence."*

Macbeth

Should the patient know the truth? What patient? let us hasten to ask, and what truth? For it is certain that there exists no general dictum or prescription for this troubled aspect of the communications between a physician and his patient. What is good medicine for the one may prove catastrophic for another, and indeed the only rule whereby the doctor may be wisely guided is for him to know the facts, know his patient, and know himself.

The doctor is more than a diagnostician and a healer; he is a bearer of tidings of salvation and doom, upon whose word hang the hope and the despair, the joy and the woe of sick and frightened patients and their kin. Grown men kiss his hands—his "golden fingers"—and behold him as some composite parent, hero and demi-god—a conception of which the doctor himself may prove at times to be an eager exponent. Thus endowed with attributes of omnipotence and omniscience it behooves him to use that power with wisdom and restraint, for should he be one of those lonely tormented souls who have entered into the domain of healing to satisfy some secret yearning to direct and control those fellow beings of whom he is covertly afraid, his words, uttered in the service of his concealed strivings may prove to be both intemperate and noxious. Such a one is given to pronouncements of the "truth" with an underlying essence of brutality, dubbed by him "frankness". He dispenses counsel where angels might fear to tread: he advises the inhibited to engage in fleshly pleasures, prescribes matrimony for the perplexed, motherhood for the depersonalized and Miami for the depressed. Indeed he is most dogmatic when he is most confused, for when he cannot be positive he most keenly feels his inner emptiness. His patient cannot be permitted to leave his presence without a diagnosis, without a prescription, nor without an injunction. For him the blurting of a reckless truth is an act of self rescue. Possessed of minimal self knowledge and hence a scant awareness of psychogenesis, he becomes irascible in the face of those illnesses which stem from the spirit. Petulantly he accuses his patient of "just talking it into yourself", (pathogenic introlalia), while angrily ordering him to "pull yourself together", (centripetal somato-traction).

*"Truth, sir, is a cow which will yield skeptics
no more milk; so they have gone to milk the bull."*

Samuel Johnson.

The obsessional physician, on the other hand, meticulously addicted to a policy of dedicated honesty, finds it incumbent upon him to convey every fact

¹ From the Department of Psychiatry, The Mount Sinai Hospital, New York City.

and every finding. Perhaps this represents in some measure a legacy from his internship days when he feared the humiliation of overlooking some physical sign detected by the hawk-eyed vigilance of the resident or chief of service. Perhaps some subsequent consultant will "show him up" again, by conveying to the sick one some abnormality overlooked by his predecessor. Whatever the basis for this insistent sharing of clinical detail the presence of an untold number of functional murmurs of the heart has been communicated to an untold number of mothers and not invariably in the absence of their children. Other point-less "truths" so confided embrace roentgenographic curiosities, mild deviations in the basal metabolic rate, questionable enlargements of ovaries, and debatably significant malpositions of the uterus.

*"Her taste exact for faultless fact amounts
to a disease."*

Mikado,
W. S. Gilbert

This obsessional commerce in "truth" finds its most widespread application in that baleful instrument—the sphygmomanometer, under the aegis of which a not inconsiderable fraction of the civilized population is currently conspiring with some elements in the medical profession in the exercise of a quasi clinical numbers racket. Figures of "140", "165", and "180" (the diastolic pressure is never cited) are bandied about like stock market quotations by individuals, who scientifically unequipped to comprehend or assimilate their significance, yet utilize them as a numerical framework of a hypochondriacal picture. The matter is all the more lamentable since the definition of normal range of blood pressure is in itself open to question and subject to periodic revision. Save for exceptional instances there would seem to be no more cogent excuse for revealing a blood pressure reading to a patient than his serum phosphatase.

This distressing consequence of the evolution of an indispensable clinical tool has its counterpart in other instances wherein the invention of diagnostic instruments and the discovery of scientific facts have contributed to the dissemination of medical mythologies under the guise of Hippocratic truth. Thus the discovery of the syndrome of acute appendicitis has given birth to that shadowy entity, the chronically diseased appendix, treated periodically by a mysterious process called "freezing". The invention of the x-ray played a not insignificant role in promoting the one-time cult of visceroptosis, leading zealous purveyors of roentgenographic gospel to subject their patients to a variety of aerobatics and abdominal appliances in an heroic endeavor to combat the malign effect of gravity upon a drooping stomach or a sagging colon. In France one gains the impression at first blush that the entire nation is afflicted with disease of the liver, which on closer inspection proves to be but a transatlantic manifestation of a national malady of our own, attributed lately to vitamin deprivation, in the recent past to "acid in the blood", and in some quarters apparently to chronic barbiturate deficiency. Indeed some medical practitioners would appear to emphasize their lofty regard for scientific truth by virtue of the respectful distance they maintain therefrom.

*"Truth does not so much good in the world as
the semblance of it does evil."*

La Rochefoucauld.

Another physician dispenses truth out of a process of psychologic projection. Wrestling with indifferent success against his own weaknesses, he may display greater vigor in combatting the temptations of his patients. Struggling manfully against his own voracity, he may, for the sake of enjoying companionship in his misery, impose stern dietary restrictions upon his marginally corpulent clientele. Such basis for prescriptions may prove especially unfortunate when the prohibitor summons his patients to enlist in his own ascetic crusade. One shudders to contemplate the thousands of thirsty victims of angina pectoris of twenty and more years ago from whom whiskey was withheld because it had not yet been learned that alcohol by mouth is an excellent dilator of the coronary arteries.

A more merciful attitude was displayed by that physician, who, having just forbidden his cardiac patient indulgence in tobacco, alcohol and amorous intimacies, was asked by the victim, "Tell me, doctor; if I give these things up, will I live longer?" To which his physician replied with charm and candor, "No, but it'll seem longer."

It does seem perplexing that so many people are still alive today, who, fifty years ago, were given but six months to live, by doctors now long since passed away. One cannot doubt that some fraction of these dire pronouncements were indeed uttered by truth-tellers with a penchant for astrological prophecy, but the suspicion is warranted that many of these recollections are instances of narcissistic chortlings by elderly hypochondriacal ladies and gentlemen, who have ever delighted in proving everyone wrong, even though it involves misquoting a physician, who, no longer on hand to dispute the accuracy, has ascribed to him a pronouncement he never made, or at least never in so vulnerable a fashion.

On the other hand there are "truths" known to patients which merit attention and respect, even when they appear absurd in the face of esteemed scientific data. An eminent surgeon, in the early days of his practice was told by a subject for hemorrhoidectomy, that he would die, if operated upon. The doctor, despite confidence in his appraisal of the patient's health and his own skill postponed the operation and reinvestigated thoroughly the man's physical status. Being fully persuaded that there was no medically discernible contraindication to this minor procedure, the surgeon performed the operation, whereupon the patient died forthwith. The autopsy failed to disclose any cause for death.

Psychiatrists are fully cognizant of the inexorable and unswerving pursuit of self destruction consciously sought for and successfully attained by those unfortunate souls imprisoned in a black hell of dark despair. Indeed the most vigilant effort proves often vain in thwarting the varied resourcefulness of a determined suicide. There is no reason to suppose, moreover, that a less conscious will to die is any the less powerful, and for this reason, our scientifically attained truths to the contrary, it is wise to heed the voice of him who prophecies

his own demise. Not long ago I urged a panic-stricken young man, suffering from a chronic pulmonary affliction, to relax a nightly vigil maintained by him in the shape of an orthopneic fright. His physician had advised me that the respiratory distress was out of proportion to the existing disease, and I assumed therefore that his nocturnal anxiety was a defense against a fear of dying. I assured him he would not die, promising him that his yielding himself up to a much needed sleep was devoid of danger. He must have been persuaded of this glib truth for he was dead within thirty-six hours.

*"The truth you speak doth lack some gentleness,
and time to speak it in; you rub the sore,
When you should bring the plaster."*

The Tempest.

A happier issue was met in the case of another young man with a pulmonary abscess, who, although he had served under fire in the Polish, French and American armies, during World War II, and had been repeatedly subjected to real threats of annihilation, asserted with complete conviction that he would perish were he operated upon. Persuasion and reassurance were of no avail, and upon my recommendation, the surgeons, ever loath to operate upon an individual so minded, waited. This was the story: While in the American army he had fallen in love with a Dutch girl, whom he made pregnant and then married. Now he was faced with two choices: to emigrate at once to the United States where he might get settled to be joined later by his wife after the birth of her child, or to remain with her until that event that they might all travel together to begin life anew on these shores. He favored the latter, but his wife urged him to go alone, which advice he reluctantly followed. Some months later he learned that a son was born, and not long thereafter that following a respiratory ailment the child had died. He grieved greatly over this, all the more because he felt that had he been on hand his contacts with American army doctors and their medicines might well have saved his son's life. No effort was made to emphasize that he like his son had a respiratory ailment and that he too must therefore die. The mere recital of this tale itself appeared to dispel his gloomy thoughts for a day or two later he confided that he had given up those "foolish ideas". Whereupon he was operated upon and did not die. I am not suggesting that death would have proved inevitable had he been operated upon at the outset. I do know, however, that experienced surgeons shy away from such undertakings if this is at all possible.

*"That which is true by lamplight is not always
true by the light of day."*

Joubert
Pensées #152

There are moreover among us those who shrink from imparting an unqualified truth because of a reluctance to become a bearer of ill tidings. In ancient times it is said that messengers bringing news of defeat from the field of battle were put to death. Even so today a physician may avoid conveying unpleasant

news lest he evoke a storm of woe and hatred in others and one of guilt within himself. If a leg or a breast must be sacrificed, however, that fact must be told, not tactlessly to be sure, but told nonetheless. The untoward effect of concealing or gilding such truths was clearly understood and graphically described by Victor Rosen (1), who was obliged to play the role of messenger in behalf of surgeons who could not bring themselves to tell a lady of 55, afflicted with a saddle embolus of the aorta, that she would have to lose her left lower extremity below the mid thigh. In the face of equivocation and evasion the patient entered into a state of dangerous manic excitement which terminated abruptly so soon as she was presented with definite, albeit tragic, truth. Not long thereafter, gangrenous changes appeared in the remaining leg, and again the surgeons, knowing that amputation of that leg too would prove necessary, hesitated to tell her so. Again symptoms of excitement made their appearance in the patient who suspected that all was not well. When informed finally that the second leg would have to be removed she quieted down, and after a day or so of depression and agitation, recovered her usual mental equanimity. "I knew it all the time," she said; "it didn't look good to me. Why don't they (the surgeons) tell me?" When it was explained that the surgeons were naturally reluctant to bear such unhappy tidings, she exclaimed, "What have they to be unhappy about?—it's my leg!"

*"My tongue hath but a heavier tale to say
I play the torturer, by small and small,
To lengthen out the worst that must be spoken."*

Richard II

In other instances, less dramatic than the foregoing, the likelihood of the eventual unfolding of the truth from one source or another, makes it often advisable to acquaint a patient with the facts as directly and simply as possible. This is true as a rule for such long standing illnesses of uncertain prognosis as multiple sclerosis. Here again concealing of the truth may not only nourish anxiety with the milk of doubt but may interfere with the capacity of the patient in his efforts to make an adjustment to a new reality.

Most vexing is the matter of truth and cancer. Here in general two attitudes prevail: to tell all and to tell nothing. Statistics are furnished by exponents of the former policy purporting to prove the soundness of their position (2), yet such reports appear to be of limited value and significance. There is told a story about a well known urological surgeon who was hospitalized a few years ago for a hypernephroma, which diagnosis had been withheld from him. One day he confided in the interne, explaining that as a mature man and an experienced surgeon there was no reason why he should not be told the truth. The interne, caught off guard, confessed the ominous diagnosis, whereupon the surgeon-patient, taking advantage of a momentary absence of a nurse, leapt to his death. The aim of a fixed policy must be directed not at some patients, nor at most patients, but at all patients, and an occasional failure condemns the entire policy. On the other hand those who practice not telling often deal in anxiety-provoking evasion and subterfuge: "You've got a bad tumor," they hint, be-

coming naïvely irascible if the word *cancer* be mentioned. Moreover a well established reputation for not telling may backfire, leading even non-cancer patients to doubt a diagnosis of benign adenoma. Some surgeons have found it useful to inform their patients that the exised lesion was "pre-cancerous"—that had it remained in situ it would have turned to cancer—a practice which appears satisfactory in many instances.

The truth of the matter—with due apology for the phrase—would indicate that there can be no policy at all, for a policy implies uniformity and uniformity is a distillate of indolence and insensitivity having no place in the practice of medicine. There is no other way to it—the doctor must know his patient, and if he believes himself incapable of so doing he should seek help. As a rule the latter is neither desirable nor practical, and a humane physician, devoting as much time to the patient as to the lesion, can often discern a proper course of action. Patients often provide broad hints that they do not want to know. A 63 year old lady, suffering from a rectal cancer, delayed consulting a physician for six months after the onset of rectal bleeding, explaining later that she thought it was her menstrual flow, although the latter had ceased some seven years before. She was making it abundantly clear that she was unwilling to face reality, and that when confronted by unpleasant and fearsome occurrences, she was quite capable of dealing successfully with them through a process of denial. Indeed she virtually proclaimed: "I don't want to know." On the other hand, following a radical mastectomy for cancer, a surgeon following his usual practice of not telling, disregarded a husband's advice to inform his wife of the diagnosis. The husband pleaded in vain with the surgeon who dismissed him with a "we know better." He was wrong, for the patient, a sensitive and perceptive person, feeling herself surrounded by duplicity and evasion, and assailed by uncertainty and doubt, became depressed and agitated, and only when she ultimately learned the truth did her spirits regain their former buoyancy, for now she knew with what she had to cope: she could fight for her life against an identified foe.

Even more painful decisions confront the physician whose patient is lingering upon the threshold of death. Here again no unswerving custom will avail, for there are those who, when told of the certitude of imminent death receive this word with a sudden tranquility and calm which mercifully replaces the anguished terror of a hopeless hope.

Writing on this issue of truth Dr. L. K. Henderson (3) observed "... The idea that the truth, the whole truth, and nothing but the truth can be conveyed to the patient is an example of false abstraction, of that fallacy called by Whitehead 'The fallacy of misplaced concreteness.' It results from neglecting factors that cannot be excluded from the concrete situation and that have an effect that cannot be neglected. Another fallacy also is involved, the belief that it is not too difficult to know the truth; but of this I will not speak further.

I beg that you will not suppose that I am recommending, for this reason, that you should always lie to your patients. Such a conclusion from what I have said would correspond roughly to a class of fallacies that I have already

referred to above. Since telling the truth is impossible, there can be no sharp distinction between what is true and what is false. But surely that does not relieve the physician of his moral responsibility. On the contrary the difficulties that arise from the immense complexity of the phenomena do not diminish, but rather increase, the moral responsibility of the physician, and one of my objects has been to describe the facts through which the nature of that moral responsibility is determined.

Far older than the precept, 'the truth, the whole truth, and nothing but the truth,' is another that originates within our profession that has always been the guide of the best physicians, and, if I may venture a prophecy, will always remain so: so far as possible, 'Do no harm.' You can do harm by the process that is quaintly called telling the truth. You can do harm by lying. In your relations with patients you will inevitably do much harm, and this will be by no means confined to your strictly medical blunders. It will also arise from what you say and what you fail to say. But try to do as little harm as possible, not only in treatment with drugs, or with the knife, but also in treatment with words, with the expression of your sentiments and emotions. Try at all times to act upon the patient so as to modify his sentiments to his own advantage, and remember that, to this end, nothing is more effective than arousing in him the belief that you are concerned wholeheartedly and exclusively for his welfare."

REFERENCES

1. ROSEN, V.: The Role of Denial in Acute Post-operative Affective Reactions Following Removal of Body Parts. *Psychosom. Med.*, 12: 356, 1950.
2. KELLY, W. D. AND FRIESON, S. R.: Do Cancer Patients Want to be Told? *Surgery*, 27: 822, 1950.
3. HENDERSON, L. J.: Physician and Patient as a Social System. *New Eng. J. Med.*, 112: 819, 1935.

THE DEVELOPMENT OF AN ACQUIRED PULMONARY CYST

HENRY J. HEIMLICH, M.D., F.A.C.S.*

INTRODUCTION

The need for additional information concerning the pathogenesis of acquired pulmonary cysts has been stressed by several authors (1, 2, 3, 4, 5, 11). The fact that numerous classifications of cystic disease of the lung exist indicates a lack of understanding of the development of these lesions (1, 11).

Most patients who require treatment for a pulmonary cyst first seek medical attention as a result of symptoms caused by the presence of the cyst. In most reported cases, thorough pulmonary studies have only been performed after the cyst is known to be present. Consequently, it is difficult to obtain information about the pathology present in the lung prior to the development of a pulmonary cyst (1, 6, 7).

An accumulation of cases demonstrating the pulmonary pathology which precedes the formation of a pulmonary cyst will lead to a clearer understanding of the pathogenesis of acquired pulmonary cysts. In one such report, Lloyd presented roentgenograms of a two-year old child demonstrating the development and spontaneous disappearance of a pulmonary cyst at the right apex (8). In that patient, the cyst occurred following the development in the left chest of pneumonia, broncho-pleural fistula, and empyema, which had resulted as a complication of measles.

The following report presents a case in which a specific lesion was known to be present at the same site from which a cyst later developed. This patient had active pulmonary tuberculosis in the right apex. Eleven years later there was radiographic evidence of healed tuberculosis in the right upper lobe and mild bronchiectasis limited to the left lung. Four years thereafter, a pulmonary cyst was seen at operation arising from the fibrotic area of healed tuberculosis in the right upper lobe.

CASE REPORT

L. A. is a 51 year old white female who was first seen in August, 1951. Her chief complaint was a chronic cough which had become increasingly severe and productive of increasing amounts of thick white and yellow sputum for one month.

Past history: The patient stated that she had had a cough since childhood. She had had scarlet fever and diphtheria as a child and for seven years thereafter had "draining ears". At the age of eighteen a tonsillectomy and submucous resection were performed and the aural drainage ceased. A report from her physician states that on October 9, 1935, she came to him complaining of a chronic cough. Physical examination revealed purulent sinusitis and fine rales in the chest over both bases. Repeated sputum examinations were negative for acid-fast bacilli until January, 1936, when a guinea pig inoculation was positive. At this time, the patient weighed 132 pounds and had occasional slight afternoon temperature elevations to 99 and 99.2. She was placed on absolute bed rest. In December, 1936, she weighed 155 pounds and chest examination revealed tuberculous activity over the right apex. The patient was followed until December, 1940, at which time her general

* From The Dept. of Surgery, The Mount Sinai Hospital, N. Y. C.



FIG. 1. Posteroanterior roentgenogram of December 26, 1947, following instillation of lipiodol into the left bronchial tree. There is an area of diffuse density in the left lower lobe. In the right apex there are infiltrations with calcified deposits.



FIG. 2. Oblique and lateral roentgenograms exposed at the same time as Fig. 1. There is cylindrical dilatation of several bronchi of the left upper and lower lobes, with sacculation of one subsegmental bronchus of the left lower lobe.

condition had improved. Roentgenograms are reported as showing no evidence of tuberculous activity.

In December, 1947, because of continued chronic cough, the patient was investigated in the Consultation Service of The Mount Sinai Hospital, New York City. Physical examination at that time was reported as showing coarse, moist, subcrepitant rales over the left lower lobe; occasional rhonchi and wheezes over the right lower lobe. Chest roentgenograms of December 26, 1947, showed an area of density and condensation of pulmo-



FIG. 3. Posteroanterior and oblique roentgenograms of January 6, 1948, following instillation of lipiodol into the right bronchial tree. There is no evidence of bronchiectasis in the right upper, middle, or lower lobes.

nary markings in the left lower lobe. In the right apex there were infiltrations with calcific deposits presumed to be the remains of an old tuberculous process (Fig. 1).

Lipidol bronchograms of the left lung taken December 26, 1947, showed cylindrical dilatation of some bronchi of the left upper and lower lobes, and sacculation present in one subsegmental bronchus of the left lower lobe (Fig. 2). Bronchograms of the right lung of January 6, 1948, revealed no evidence of bronchiectasis in the right upper, middle, or lower lobes (Fig. 3). The diagnosis was chronic sinusitis and bronchiectasis. Surgery was not recommended because of the patient's age and the mildness of the process.

Present Illness: Until April 1951, the patient's symptoms were unchanged. At that time she noted pink sputum for the first and only time. During August, 1951, her cough became increasingly severe and productive of larger amounts of white and yellow sputum. She was hospitalized on September 4, 1951.

Physical Examination: A well-nourished, well-developed female not appearing acutely or chronically ill. B.P. 118/90; P 88; T 100.4; R 20. There were no enlarged lymph nodes. The thyroid was palpable and slightly enlarged. Pulmonary examination showed scattered post-tussic inspiratory rales at the left base posteriorly and slightly diminished breath sounds at the right apex. The heart was not enlarged, no murmurs were present, and the rhythm was regular. The remainder of the examination was not contributory.

Laboratory Data: Hgb 12.5; RBC 4.3; WBC and differential normal. Urine examination negative. FBS 102; BUN 17. Serology negative. Concentrations and cultures for acid-fast bacilli were negative on three sputa, one gastric, and one urine specimen. Tuberculin skin test 1:10,000 was positive.

Radiographic Studies: Chest roentgenograms of August 6, 1951, and October 16, 1951, show a diffuse haziness over the left lower chest. A transverse band of increased density containing small calcified nodules is present on the right, crossing the chest at the level of the lower edge of the first rib anteriorly. No lung markings are seen above this level (Fig.



FIG. 4. Posteroanterior roentgenogram of August 6, 1951. The diffuse density in the left lower lobe persists. A transverse band of increased density containing small calcified nodules is present on the right, crossing the chest at the level of the lower edge of the first rib anteriorly. No lung markings are seen above this level.

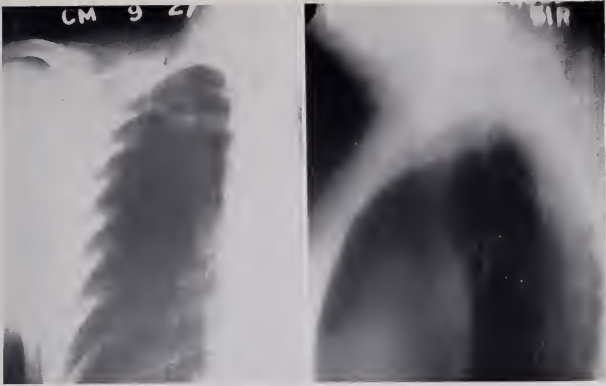


FIG. 5. Tomograms of September 27, 1951, demonstrating more clearly the findings in Fig. 4. A. Anteroposterior tomogram at level 6 centimeters. B. Right lateral tomogram at level 12 centimeter.



FIG. 6. Posteroanterior roentgenogram, eleven months after operation. The right lung is fully expanded. The fine calcifications in the right upper lobe are now adjacent to the mediastinum. The diffuse density over the left lower lobe persists.

4). There is no change in the roentgenograms between August 6, 1951, and October 16, 1951. The above findings are demonstrated more clearly by antero-posterior and lateral tomograms of September 27, 1951 (Fig. 5).

Course: Prior to hospitalization, the patient had been given a course of penicillin for one week which caused no change in symptoms or radiographic findings. Bronchoscopy showed the right upper lobe bronchial mucosa reddened and edematous. Divisions of the right upper lobe were patent but compressed from without. There was considerable mucopurulent sputum in both main bronchi. On October 9, 1951, streptomycin 1.0 Gm. and PAS 12.0 Gm. daily were started as tuberculosis could not be ruled out. Thereafter, the cough subsided markedly and the sputum entirely disappeared.

Operative Procedure and Findings: On November 14, 1951, a right thoracotomy was performed. The patient was intubated and placed in the lateral position. The chest was entered through a right postero-lateral thoracotomy incision with resection of the fifth rib. The right middle and lower lobes appeared normal and had no adhesions to the chest wall and no evidence of emphysema or fibrotic nodules. The entire lung collapsed with a normal elasticity and expanded readily. In the apex of the pleural cavity an air-containing cyst was found approximately seven centimeters in diameter which inflated when the lung was inflated and collapsed only slightly when the lung was allowed to collapse. This cyst had a smooth surface. It was firmly attached to the apex of the pleural cavity at one point over an area of approximately one centimeter from which it was freed extrapleurally. The largest portion of the cyst wall was free and unattached. An area of the cyst, approximately three centimeters in diameter, was attached to the lung. One-third of this diameter could easily be freed by dividing its loose fibrous attachment to the surface of the lung. An area two centimeters in diameter, which was firmly attached to the lung, appeared to represent the site on the right upper lobe from which the cyst originated. This site was in the center of a dense fibrous plaque which contained small calcified nodules appearing to be a healed tuberculous lesion. In the roentgenograms this area is seen as a linear density. The lung was clamped across the two centimeter attachment and the cyst was removed intact. The small cut surface of the lung was then ligated with silk.

The lung expanded except for the small fibrous area and easily filled the pleural cavity. A tube was inserted through the eighth intercostal space for underwater drainage and the chest was closed in layers.

Pathological Report: Cyst of the lung measuring $7 \times 2 \times 0.75$ centimeters. The thin cyst wall consisted of fibrous tissue without epithelial lining. There was a two centimeter area of adherent greyish pulmonary tissue. No bronchial connection was visualized.

Follow-up: Recovery was uneventful. The patient returned to work two months after operation. She still has a cough similar to that which she had prior to the existence of the cyst but less severe than that experienced when the cyst was present. Her general condition is excellent.

A chest roentgenogram taken eleven months following her operation shows that the right lung has remained clear and fully expanded. The fine calcifications in the right upper lobe are seen to be adjacent to the mediastinum. The haziness over the left lower lung field is still present and unchanged (Fig. 6).

COMMENT

This patient had pulmonary tuberculosis involving the right apex when she was thirty-six years of age. Eleven years later, roentgenograms showed a healed fibrotic and calcified tuberculous lesion in the right upper lobe. Bronchograms at this time showed no bronchiectasis on the right side, but slight dilatation of bronchi of both lobes on the left, with sacculation of one subsegmental bronchus of the left lower lobe. Rales were a constant finding in the left lower lobe throughout her history. Chronic sinusitis and bronchiectasis were diagnosed as the

cause of a chronic cough. Four years thereafter, a cyst was found at the right apex originating from the site of the old healed tuberculous lesion. This cyst was in itself the cause of a more severe productive cough due to compression of the right upper lobe. In this patient, as in Lloyd's case (8), the disease which caused the cough was limited to the left side, whereas the cyst developed at the right apex.

DISCUSSION AND CONCLUSIONS

The development of acquired pulmonary cysts has been frequently attributed to a valvular mechanism partially obstructing the bronchus. Air, trapped in the lung by this obstruction, is said to create an increased intra-alveolar tension which stretches and ruptures alveolar walls. This situation could result from one of the following conditions: the swelling of the bronchial walls and partial obstruction of the bronchus by thick secretions in chronic bronchitis, various types of emphysema, spasm of the bronchial muscles in asthma (6), tortuosity of respiratory bronchioles and a flaplike valve action of tissue surrounding an air passage (7). Necrosis of alveolar walls due to pneumonia or lung abscess has also been described as preceding the formation of emphysema with subsequent cyst formation.

In 1935, Moolten (9) described an experiment in which a local laceration of the fibroelastic framework was made through the bronchus of isolated human and animal lungs. Inflation of these lungs by positive intrabronchial pressure caused the formation of a round air-containing cystic or cavity-like structure at the site of laceration. The size of the cysts was dependent on the amount of pressure applied during inflation rather than on the size of the laceration. (Similarly, a large cyst may have either a narrow or broad site of origin from the lung.) This experiment demonstrated that an area of permanently reduced resistance to inflation, when present in a lung, will form a round cystic structure, (except where limited by surrounding structures), when the intrabronchial pressure is increased beyond the resistant strength of the weakened area. In applying these experimental results to the case herein presented, the healed tuberculous lesion in the right upper lobe represents an area of reduced resistance to inflation. When this area was exposed to the repeated increased intrabronchial pressures caused by a chronic cough, a cyst resulted.

Moolten (9), in discussing the physical laws of the transmission of pressure within a fluid (or gas), argued that the increase of pressure within a fluid (or gas) is transmitted equally in all directions. He concluded, therefore, that any defect in the lung tends to assume a spherical contour during inflation and will grow in size until the elastic resistance of its wall equals that of the remainder of the lung at any given level of intrapulmonary pressure. It follows, that the cyst or cavity will persist as long as some degree of lung expansion is present.

An area of decreased resistance to inflation could conceivably be produced by the following pathologic conditions: a healed tuberculous lesion, emphysema of a localized or generalized nature, acute infection, an area of fibrosis or necrosis resulting from a previous infection, or a congenital defect. The increased intra-

bronchial pressure which can cause a cyst to develop in such a weakened area may be due to an acute or chronic cough, not necessarily related to the pathology at the site from which the cyst develops. Other causes of intrabronchial pressure are straining and crying.

There are two factors which may explain why a cyst remains distended in the intervals when the intrabronchial pressure is not increased. In accordance with the physical laws of the transmission of pressure within a gas, when air is present in the bronchial system under sufficient pressure to keep the lung inflated, the site of least resistance to inflation, i.e., the cyst, cannot collapse. Secondly, the tissue which forms the cyst wall is less elastic than that of the normal lung. It may consist of stretched, thinned-out pulmonary tissue, visceral pleura, fibrous tissue, or a combination of these. Therefore, the cyst will not have a tendency to contract to any great extent when the intrabronchial pressure is lessened.

Recently, Mayer and Rappaport have outlined a new concept indicating that there is a common origin of cystic, bronchiectatic, and emphysematous lung changes (10). They suggest that abnormal air spaces may develop on the basis of developmental defects that have arisen during the postnatal period of growth of the lungs. These abnormal air spaces may or may not be clinically detectable at the time of formation, but may progress to the clinical pictures typical of older age groups. Such clinical findings are bronchitis and various degrees of bronchiectasis seen in childhood, bullous structures and dry bronchiectatic lesions of young adults, and infection or emphysema, or a combination of these which may be present in middle adult life. The course of the patient herein presented demonstrates the conditions found in both the childhood and young adult years. Mayer and Rappaport's concept rejects the purely mechanical principles which have been postulated. Rather, it is based on a biological principle that a part of the visceral function of normal lung is the partitioning of air spaces. These authors maintain that cysts, bronchiectasis, and emphysema result from a disorder of this function due to lack of alveolar structure in lung defects of developmental or pathological origin (11).

SUMMARY

1. The development of an acquired pulmonary cyst is presented in a patient whose history and roentgenologic reports are traced fifteen years prior to the development of the cyst. An extensive roentgenologic study was also made four years before the appearance of the cyst. The pulmonary status which preceded the formation of the cyst is described.

2. The pathology of this cyst and of the lung is described as found at operation.

3. The history, roentgenograms, and findings are correlated with the findings and concepts of other authors in a consideration of the pathogenesis of acquired pulmonary cysts.

REFERENCES

1. COOKE, N., AND BLADES, B.: Cystic Disease of the Lungs. *J. Thoracic Surg.*, 23: 546, 1952.

2. MOOREMAN, L. J.: Chapter on Cystic Disease of the Lungs. *The Chest and the Heart*, by Myers and McKinty, Springfield, Ill., 1948, Charles C. Thomas, Vol. 1, 578.
3. BOYD, W.: *Surgical Pathology: On Cystic Disease of the Lung*. Philadelphia, 1947, W. B. Saunders Company, 799.
4. DUGAN, D. J., AND SAMSON, P. C.: The Surgical Treatment of Giant Emphysematous Blebs and Pulmonary Tension Cysts. *J. Thoracic Surg.*, 20: 729, 1950.
5. HOLLINGSWORTH, R. K., ELOESSER, L., AND AVERY, E. E.: Discussion of a Paper by Dugan and Samson. *J. Thoracic Surg.*, 20: 729, 1950.
6. HEAD, J. H., AND AVERY, E. E.: Intracavitary Suction (Monaldi) in the Treatment of Emphysematous Bullae and Blebs. *J. Thoracic Surg.*, 18: 761, 1949.
7. ALLBRITTEN, F. F., AND TEMPLETON, J. Y., III: Treatment of Giant Cysts of the Lung. *J. Thoracic Surg.*, 20: 749, 1950.
8. LLOYD, M. S.: Bullous Emphysema; A Case Report. *J. Thoracic Surg.*, 18: 532, 1949.
9. MOOLTEN, S. E.: Mechanical Production of Cavities in Isolated Lungs. *Arch. Path.*, 19: 825, 1935.
10. MAYER, E., AND RAPPAPORT, I.: Developmental Origin of Cystic, Bronchiectatic and Emphysematous Changes in Lungs: New Concept. *Dis. Chest*, 21: 146, 1952.
11. MAYER, E., AND RAPPAPORT, I.: Clinical Observations and Interpretations of Abnormal Air Spaces in the Lungs. *J. A. M. A.*, 153: 700, 1953.

THE CAPACIGRAPH, AN INSTRUMENT FOR RECORDING CARDIAC OUTPUT

HUBERT MANN, M.D.*

The year 1954 marks a half century of fruitful cardiac research which was in great part due to the development of the clinical electrocardiograph. We have learned many things about the tiny amount of electrical current produced by the beating heart and have been able by a study of electrical potentials to derive much useful information about the physiological and pathological functions of normal and diseased hearts. During the past few years the study of clinical electrocardiography has apparently reached the stage of diminishing returns. It is now a standardized, routine office procedure, of immense clinical value, but this field has been thoroughly explored by countless investigators and seems to have yielded us its major benefits.

During the past few years the focus of cardiac research has shifted from a study of the electrical output of the heart to the mechanical concept of the heart as a pump with various valves and chambers which function in a more or less efficient fashion. After all the prime function of the heart is to pump blood and its other activities are secondary to this main purpose. The study of congenital malformations, valvular lesions and myocardial impairments has resulted in numerous mechanical and surgical measures which have been undertaken or proposed with the definite object of improving the mechanical efficiency of the heart.

This study has been rendered difficult by the fact that today we have no simple clinical method of measuring or recording the mechanical function of the heart. Various mathematical formulae based on heart rate and blood pressure have failed to fill this gap. Ballistocardiography, which antedated electrocardiography, has received increasing attention but still leaves much to be desired. The polygraph now has only historical interest. Cardiac catheterization has come to the fore lately, but it has the disadvantages of being complex, cumbersome and not always harmless. It cannot be considered a simple clinical procedure for office use.

The ideal instrument should provide a simple, safe method of recording the mechanical work of the heart, a method so simple that it can be used by the average clinician, and as safe as the taking of routine electrocardiograms. It should be not merely free from danger, but it should operate without producing any sensations or conditions which may affect or alter the heart itself.

Fortunately the contractions of the heart with resulting movements of the blood do produce an effect which can be observed and recorded simply and with complete safety. This effect, known as an alteration in electrical capacitance can be recorded by a small instrument, an alternating current bridge, which is about as simple in operation as an ordinary electrocardiograph. The instrument, which is connected to the patient by two electrodes such as are used in electro-

* 1150 Fifth Ave., New York, N. Y.

cardiography, produces a curve on standard cardiograph paper. It weighs about nine and one-half pounds and is operated by adjusting it to the patient much as a radio or television set is tuned to a station. This instrument I have called a capacigraph.

When the capacigraph is adjusted to match the electrical impedance of the part of the body under investigation, in this case the thorax, then any change in size, shape or blood distribution in this part of the body will result in a change in electrical equilibrium, producing a curve which can be observed and recorded. The rhythmic contractions of the heart produce a curve of characteristic form, called a capacigram.

Each time the heart beats there is a movement of blood from the chambers of the heart into the great vessels, the lungs and the peripheral circulation. This recurring redistribution of blood produces alterations in the size and contour of the heart, blood vessels, lungs and peripheral areas. Every such alteration in the circulating blood produces alterations in the electrical capacitance of the tissues involved. These alterations in capacitance are synchronous with various phases of the heart beat and can be distinguished easily from alterations caused by respiratory or muscular activity. Study of such alterations in the thorax brings us very close to the actual mechanical operations of the heart because these alterations in capacitance are produced by the blood which the heart ejects. It can readily be understood that the greater the volume of blood ejected the more marked will be these changes and that the more rapidly the blood is ejected the more rapidly the changes will take place.

Figure 1 shows the type of curve produced by an individual with a perfectly functioning heart. This patient, a woman in the early thirties has swum the English Channel three times, holds the world's record for the Catalina Island swim and has performed many other swimming feats. She has never had a day's illness and swims at least one hour each day. Physical examination is entirely normal except for slight cardiac enlargement. Electrocardiogram is normal. I have selected this record as normal because of the obvious excellent circulatory condition of this patient. The curve is obtained by connecting the capacigraph to electrodes on the right and left arm of the patient and instructing the patient to stop breathing for about six seconds. Standardization deflections are produced



FIG. 1

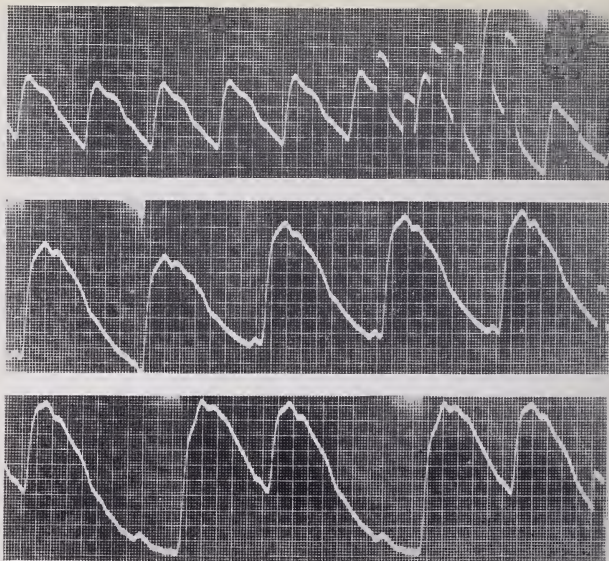


FIG. 2

at the end of the record by introducing into the circuit a small measured capacitance (10 micromicro farads). The normal capacigram is characterized by a large, smooth peak, several centimeters high, corresponding to ventricular systole. This peak takes about .12 to .14 seconds to rise to its highest point and then descends gradually with one or several "Katacrotic" notches. This curve is repeated with each heart beat.

Figure 2 shows capacigrams of a man of 60 who has a heart of normal size and shape, but who has a transient atrioventricular conduction defect of varying

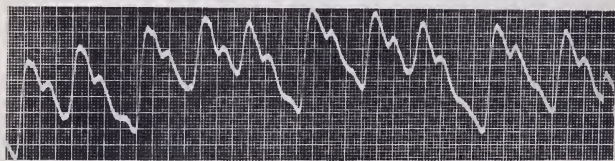


FIG. 3

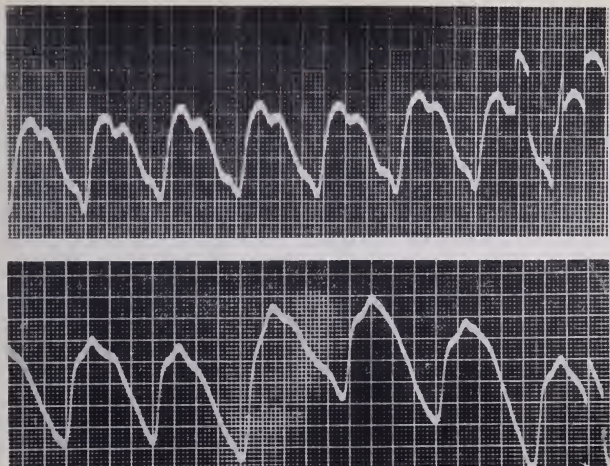


FIG. 4

degree. The upper curve shows regular sinus rhythm with a rate of 67 per minute. The middle curve shows a two to one block with a ventricular rate of 38 per minute. The lower curve shows a variable block. Note that the height of the main deflection increases with increasing intervals between beats (increasing cardiac output) as does the duration of the main up-stroke.

Figure 3 is a capaciogram of a patient with atrial fibrillation. Note that the height of the main deflection varies greatly in successive beats and that in general longer interventricular intervals with more adequate filling and emptying of the ventricles produce higher deflections.

Figure 4 shows two capaciograms of patients with congenital cardiac defects (patent interventricular septum). Note the slow development and unusual shape of the main deflection.

The curves shown are chosen to illustrate the fact that various changes in cardiac dynamics produce decided alterations in the capaciogram, changes of a type susceptible to analysis and classification. Valvular lesions, cardiac hypertrophy, myocardial impairment and many other conditions produce marked alterations in the capaciogram. In general conditions which increase cardiac output produce high deflections while decreased output per beat results in low deflections. Slow or delayed expulsion of blood produces a slowly rising curve while rapid expulsion has the opposite effect. For these reasons the capaciograph offers us a safe, simple and reproducible method of studying cardiac dynamics in clinical practice.

SUMMARY

The changing aspect of cardiac research calls for an instrument capable of recording the action of the heart as a pump. By means of a new instrument, the capacigraph, a permanent record of cardiac activity can be obtained. The nature of the capacigraph is outlined and several characteristic curves or capacigrams are shown. This curve is seen to have a definite correlation with cardiac ejection. The capacigraph offers a new and potentially valuable method of studying cardiac dynamics clinically.

INDEX TO VOLUME TWENTY

The letters "ab" preceding the page number indicate an abstract.

- ABDOMINAL** adhesions in rats, failure of repeated intraperitoneal injection of hyaluronidase to prevent recurrence of, (R. J. Wilder), 278
- Abrams, J., et al., The use of radioactive gold in the treatment of effusions due to cancer, 237
- Abramson, H. A., Aerosols, the role of particle size in inhalation therapy by atomization and by penicillin dusts, ^{ab}76
- Accessory lung—unusual variations (G. P. Seley), 263
- Acelman, M. H., et al., A method of automatic controlled respiration for anesthesia in the dog, ^{ab}81
- ACTH, cortisone and sodium salicylate, suppression of the phenomenon of local tissue reactivity by, (G. Schwartzman), ^{ab}74
- Adelman, N., et al., Shortening of bleeding time by a water-soluble adrenochrome derivative, ^{ab}84
- Adenomas of the colon and rectum, (R. Turell and R. S. Wilkinson), ^{ab}75
- Adhesions abdominal in rats, failure of repeated intraperitoneal injection of hyaluronidase to prevent recurrence of, (R. J. Wilder), 278
- Adrenal cortex in liver disease, (J. J. Webster), ^{ab}76
- Aerosols, the role of particle size in inhalation therapy by atomization and by penicillin dusts, (H. A. Abramson), ^{ab}76
- Afibrinogenemia in pregnancy: diagnosis and treatment, (H. Chessin and J. C. Greenwald), 263
- Allantoic fluid of mumps virus hemagglutination, role of the erythrocyte in inhibition by, (A. L. Florman), ^{ab}73
- Alper, J., et al., Inflammatory diseases of the gastrointestinal tract; clinical conference, 58
- Amphetamine (benzedrine) sulfate and picrotoxin in barbiturate intoxication, the combined use of, (B. W. Willow), ^{ab}72
- Amputations for gangrene in diabetics, results of midleg, (S. Silbert and H. Ilaimovici), ^{ab}74
- Angina pectoris, The ineffectiveness of Khellin in the treatment of, (G. C. Leiner and S. Daek), 41
- Ankylosis, temporomandibular, bilateral, (G. P. Seley, et al.), 145
- Anosognosia, the syndrome of, (E. A. Weinstein and R. L. Kahn), ^{ab}86
- Antibiotic therapy, The importance of the laboratory in, (S. S. Schneierman and M. S. Bryer), 155
- The limitations of the laboratory, (B. M. Wagner), 339
- Antihistaminic drugs in producing cross-sensitization dermatitis, the role of the, (S. M. Peck), ^{ab}78
- Aortic arch, right-sided, (P. Samet and D. J. Stone), ^{ab}84
- Arthritis, rheumatoid, deoxycortone and ascorbic acid in, (S. Davidson), ^{ab}82
- Ascorbic acid and deoxycortone in rheumatoid arthritis, (S. Davidson), ^{ab}82
- Atherosclerosis: A problem in newer public health, (A. Keys), 118
- Aufses, A. H., Primary carcinoma of the lung, 212
- Aureomycin, pruritus vulvae due to, (H. T. Behrman), ^{ab}76
- therapy in primary atypical pneumonia, an evaluation of, (E. B. Schoenbach, A. Sweed, B. Tepper, and M. S. Bryer), ^{ab}79
- BACITRACIN** in rabbits, The effect of intraneural injection of, (P. Teng and S. Gross), 46
- further experiences in treatment of septic meningitis with, (P. Teng), ^{ab}85
- Bacteremia and bacterial endocarditis, postoperative, penicillin prophylaxis of, (P. A. Lichtman, et al.), ^{ab}83
- Bacterial infections, Problems in the treatment of refractory, (M. S. Bryer and S. S. Schneierman), 285
- Bakst, A., et al., Inflammatory diseases of the gastrointestinal tract: clinical conference, 58
- Barbiturate intoxication, the combined use of picrotoxin and amphetamine (benzedrine) sulfate in, (B. W. Willow), ^{ab}72
- Behrman, H. T., Pruritus vulvae due to aureomycin, ^{ab}76
- Bellwin, A., et al., Granulosa cell tumor, 229
- Bernheim, A. I., et al., Inflammatory diseases of the gastrointestinal tract: clinical conference, 58
- Besson, G., et al., Studies in myasthenia gravis: Edrophonium chloride (tensilon) test as a new approach to management, 165
- Bick, E. M., Healing of fractures, ^{ab}81
- Longitudinal growth of the human vertebra, ^{ab}72
- Bilateral abnormality in the electroencephalogram, The significance of, (M. Ostow and H. Strauss), 173
- Billow, B. W., The combined use of picrotoxin and amphetamine (benzedrine) sulfate in barbiturate intoxication, ^{ab}72
- Bing, R. J., The metabolism of the human heart in vivo, 100
- Birnbaum, A., et al., Films of omega-branched fatty acids, ^{ab}85

- Bleeding time by a water-soluble adrenochrome derivative, shortening of, (H. Sobotka and N. Adelman), ^{ab}84
- Blood exchange in replacement transfusions, studies with erythrocytes tagged with radioactive phosphorus, (L. R. Wasserman, I. A. Rashkoff, L. Sharney, Tse-Fei Yoh, and D. Leavitt), ^{ab}75
- exchange in replacement transfusions, theoretic considerations, (L. R. Wasserman and L. Sharney), ^{ab}75
- factors, newer knowledge of human, (R. E. Rosenfield and P. Vogel), 89
- levels of I-131 after tracer doses in the diagnosis of hyperthyroidism, (S. Silver and M. H. Fieber), ^{ab}79
- urea nitrogen, a rapid method for determination of (H. Lear), ^{ab}82
- Blum, L., et al., A method of automatic controlled respiration for anesthesia in the dog, ^{ab}81
- Bowel, lower, an evaluation of present day surgical procedures in diseases of the, (R. Turell and R. S. Wilkinson), ^{ab}85
- Brahms, S. A., et al., An experimental study of the cardiovascular effects of diodrast, ^{ab}77
- Brain, correlation of clinical and EEG abnormalities in tumors and vascular disease of the brain, (E. A. Weinstein, et al.), ^{ab}86
- tumors in infancy and childhood, (S. W. Gross), ^{ab}73
- Bruch, H., Psychosomatic Aspects of Obesity, 1
- Bryer, M. S., et al., An evaluation of aureomycin therapy in primary atypical pneumonia, ^{ab}79
- Problems in the treatment of refractory bacterial infections, 285
- Bryer, M. S., et al., The importance of the laboratory in antibiotic therapy, 155
- C**ANCER, effusions due to, the use of radioactive gold in the treatment of, (N. Simon, et al.), 237
- Capacigraph: An instrument for recording cardiac output, (H. Mann), 360
- Carcinoma of the stomach, differentiation from: localized hypertrophied gastric folds, (S. I. Gurman and B. S. Wolf), 315
- of the stomach following surgery for chronic duodenal ulcer, (D. Orringer), ^{ab}74
- of the pancreas, post-bulbar duodenal obstruction in, (R. H. Marshak, et al.), ^{ab}83
- Primary of the lung, (A. H. Aufses), 212
- Carcinomas, metachronous, of the duodenum and the colon, (G. J. Lesnick), 140
- Cardiac cycle, electrokymographic studies of the normal, (H. Mednick, J. B. Schendel, and P. Samet), ^{ab}72
- output, the capacigraph, An instrument for recording, (H. Mann), 360
- Castration complex, some gynecological implications of the, (B. C. Meyer), 267
- Chanley, J. D., et al., Dextrorotary acids of tubercle bacilli lipids, ^{ab}72
- Chessin, H., et al., Afibrinogenemia in pregnancy: diagnosis and treatment, 263
- Churg, J., et al., Multiple myeloma: lesions of the extraosseous hematopoietic system, ^{bs}73
- Cod liver oil ointment therapy in proctologic disorders (R. Turell), ^{ab}75
- Collagen content of guinea pig tissues, (S. K. Elster and E. L. Lowry), ^{ab}73
- Colon and duodenum, metachronous carcinomas of the, (G. L. Lesnick), 140
- and rectum, adenomas of the, (R. Turell and R. S. Wilkinson), ^{ab}75
- Colp, R., et al., Inflammatory diseases of the gastrointestinal tract: clinical conference, 58
- Cornell, A., et al., Partial gastric resection for peptic ulcer of the esophagus, ^{ab}82
- Cortisone, ACTH and sodium salicylate, suppression of the phenomenon of local tissue reactivity by, (G. Schwartzman), ^{ab}74
- upon poliomyelitis infection, enhancing effect of, (G. Schwartzman), ^{ab}84
- Cranin, N., et al., Bilateral temporomandibular ankylosis, 145
- Crohn, B., et al., Inflammatory diseases of the gastrointestinal tract: clinical conference, 58
- Crowder, C. H., et al., Measurement and significance of urinary appearance time in the dog, ^{ab}78
- Cyst, pulmonary, The development of an acquired, (H. J. Heimlich), 351
- retroperitoneal (metanephrogenic). Absence of right kidney, (G. D. Oppenheimer and J. M. Silagy), 324
- D**ACK, S., et al., The ineffectiveness of Khellin in the treatment of angina pectoris, 41
- Davidoff, L. M., The medical teaching mission to Israel and Iran, 280
- Davids, A., et al., Hystero-graphy and hysterosalpingography, ^{ab}77
- Davison, S., Deoxycortone and ascorbic acid in rheumatoid arthritis, ^{ab}82
- Deoxycortone and ascorbic acid in rheumatoid arthritis, (S. Davison), ^{ab}82
- Dermatitis, the role of antihistaminic drugs producing cross-sensitization, (S. M. Peck), ^{ab}78
- Diabetics, results of midleg amputations for gangrene in, (S. Gilbert and H. Haimovici), ^{ab}74
- Diagnosis and treatment, afibrinogenemia in pregnancy, (H. Chessin and J. C. Greenwald), 263
- Diodrast, an experimental study of the cardiovascular effects of, (A. J. Gordon, S. A. Brahms, S. Megibow, and M. L. Sussman), ^{ab}77

- Disease and health in the scalp, (H. T. Behrman), 236
- Dreiling, D. A. Sr., et al., Inflammatory diseases of the gastrointestinal tract: clinical conference, 58
- Dreiling, D. A., et al., Post-bulbar duodenal obstruction in carcinoma of the pancreas, ^{ab}83
- Duodenum and the colon, metachronous carcinomas of the, (G. J. Lesnick), 140
- Duodenal, post-bulbar, obstruction in carcinoma of the pancreas, R. H. Marshak, D. A. Dreiling, and A. I. Friedman), ^{ab}83

- E**DROPHONIUM chloride (tensilon) test as a new approach to management, Studies in myasthenia gravis, (K. E. Osserman, L. I. Kaplan, and G. Besson), 165
- Effusions due to cancer, The use of radioactive gold in the treatment of, (N. Simon, et al.), 237
- Electroencephalography, clinical, (M. Ostow), ^{ab}79
- Electroencephalogram, The significance of bilateral abnormality in the, (M. Ostow and H. Strauss), 173
- Electrokymographic studies of the normal cardiac cycle, (H. Mednick, J. B. Schendel, and P. Samet), ^{ab}72
- Eliasoph, J., et al., The use of radioactive told in the treatment of effusions due to cancer, 237
- Elster, S. K., et al., Collagen content of guinea pig tissues, ^{ab}73
- Emotional factors in the etiology and therapy of hyperthyroidism, (T. Lidz), 27
- Endocarditis, bacterial, and bacteremia, postoperative, penicillin prophylaxis of, ^{ab}83
- Epstein, W. A., et al., Value of hysterography in the diagnosis of large submucous uterine fibroids, ^{ab}78
- Equipment of new and remodeled areas, six principles of purchasing for the, (M. R. Steinberg), ^{ab}75
- Erythrocyte in inhibition by allantoic fluid of mumps virus hemagglutination, role of the, (A. L. Florman), ^{ab}73
- Erythropoiesis, The stimulus for, (W. S. Root), 331
- Esophagus, partial gastric resection for peptic ulcer of the, (A. Cornell and A. Winkelstein), ^{ab}82
- Etiology and therapy of hyperthyroidism, emotional factors in the, (T. Lidz), 27

- F**ATTY acids, films of omega-branched, (H. Sobotka, S. Rosenberg, and A. Birnbaum), ^{ab}85
- Fenestration operation, tympanomeatal membrane in the, (S. Rosen), ^{ab}84
- by cold fracture method: preliminary report of an improved technique, (S. Rosen), ^{ab}74
- surgery, teaching, (S. Rosen), ^{ab}78

- Fibroids, uterine, large submucous, value of hysterography in the diagnosis of, (R. H. Marshak, et al.), ^{ab}78
- Fieber, M. H., et al., Blood levels of I-131 after tracer doses in the diagnosis of hyperthyroidism, ^{ab}79
- Fishman, A. P., et al., Measurement and significance of urinary appearance time in the dog, ^{ab}78
- Fistulous openings into the gastrointestinal tract, psychophysiological studies of, (S. G. Margolin), 194
- Florman, A. L., An introduction to the pathogenesis of viral infections, 309
- Fractures, healing of, (E. M. Bick), ^{ab}81
- Friedman, A. I., et al., Megacolon, a complication of ulcerative colitis, ^{ab}83
- Post-bulbar duodenal obstruction in carcinoma of the pancreas, ^{ab}83

- G**ANGRENE in diabetics, results of mid-leg amputations for, (S. Silbert and H. Haimovici), ^{ab}74
- Gastric folds, Localized hypertrophied: differentiation from carcinoma of the stomach, (S. I. Gurman and B. S. Wolf), 315
- Gastrointestinal tract, Psychophysiological studies of fistulous openings into the, (S. G. Margolin), 194
- Inflammatory diseases of the: clinical conference, (F. King, et al.), 58
- Goldberger, M. A., et al., Granulosa cell tumor, 229
- Hystero-graphy and hysterosalpingography, ^{ab}77
- Value of hysterography in the diagnosis of large submucous uterine fibroids, ^{ab}78
- Goldman, I. B., A new nasal splint, ^{ab}82
- Gomez, D. M., et al., Measurement and significance of urinary appearance time in the dog, ^{ab}78
- Gordon, A. J., et al., An experimental study of the cardiovascular effects of diodrast, ^{ab}77
- Multiple myeloma: lesions of the extra-osseous hematopoietic system, ^{ab}73
- Granulosa cell tumor, (A. Bellwin and M. A. Goldberger), 229
- Greenwald, J. C., et al., Afibrinogenemia in pregnancy: diagnosis and treatment, 263
- Gross, S. W., Brain tumors in infancy and childhood, ^{ab}73
- Gross, S., et al., The effect of intraneural injection of bacitracin in rabbits, 46
- Gurman, S. I., et al., Localized hypertrophied gastric folds: differentiation from carcinoma of the stomach, 315
- The use of radioactive gold in the treatment of effusions due to cancer, 237
- H**AIMOVICI, H., et al., Results of mid-leg amputations for gangrene in diabetics, ^{ab}74

- Hammerman, D. J., et al., Some clinical experience in the use of Triethylene Melamine (T.E.M.), 16
- Health and disease in the scalp, (H. T. Behrman), 236
- Heart, human, *in vivo*, the metabolism of the, (R. J. Bing), 100
- Heimlich, H. J., The development of an acquired pulmonary cyst, 351
- Hirsh, J., Revelations from the early annual reports of the Mount Sinai Hospital, 151
- Hollander, F. et al., The diagnostic significance of urinary pepsinogen excretion in diseases of the upper gastrointestinal tract, ^{ab}82
- Hulse, W. C., Therapeutic management of group tension, ^{ab}73
- Human blood factors, newer knowledge of, (R. E. Rosenfield and P. Vogel), 89
- heart, *in vivo*, the metabolism of the, (R. J. Bing), 100
- Hyaluronidase, failure of repeated intraperitoneal injection of, to prevent recurrence of abdominal adhesions in rats, (R. J. Wilder), 278
- Hydrocarbon-stearic acid mixtures, films of, (H. Sobotka and S. Rosenberg), ^{ab}84
- Hyperthyroidism, blood levels of I-131 after tracer doses in the diagnosis of, (S. Silver and M. H. Fieber), ^{ab}79
- emotional factors in the etiology and therapy of, (T. Lidz), 27
- Hystero-graphy, value of, in the diagnosis of large submucous uterine fibroids, (R. H. Marshak, M. A. Goldberger, and W. A. Epstein), ^{ab}78
- I**NFECTIONS, bacterial, Problems in the treatment of refractory, (M. S. Bryer and S. S. Schneierson), 285
- viral, An introduction to the pathogenesis of, (A. L. Florman), 309
- Inflammatory diseases of the gastrointestinal tract: clinical conference (F. King et al.), 58
- Inhalation therapy by atomization and by penicillin dusts, the role of particle size in, aerosols, ^{ab}76
- Intoxication, barbiturate, the combined use of picrotoxin and amphetamine (benzedrine) sulfate in, (B. W. Billow), ^{ab}72
- Intraneural injection of bacitracin in rabbits, The effect of, (P. Teng and S. Gross), 46
- Isodose curves, clinical (R. Loevinger, B. S. Wolf, and W. Minowitz), ^{ab}83
- Israel and Iran, The medical teaching mission to, (L. M. Davidoff), 280
- J**ANOWITZ, H. D. et al., The diagnostic significance of urinary pepsinogen excretion in diseases of the upper gastrointestinal tract, ^{ab}82
- K**AHN, R. L., et al., Correlation of clinical and EEG abnormalities in tumors and vascular disease of the brain, ^{ab}86
- The syndrome of anosognosia, ^{ab}86
- Kaplan, L. I., et al., Studies in myasthenia gravis: Edrophonium chloride (tensilon) test as a New Approach to Management, 165
- Kaufman, M. R., An integration of the psychosomatic viewpoint in medicine, 247
- Keys, A., Atherosclerosis: A problem in newer public health, 118
- Khellin, The ineffectiveness of, in the treatment of angina pectoris, (G. C. Leiner and S. Dack), 41
- Khilnani, M., et al., The use of radioactive gold in the treatment of effusions due to cancer, 237
- Kidney, absence of right: retroperitoneal (metanephrogenic) cyst, (G. D. Oppenheimer and J. M. Silagy), 324
- King, F., et al., Inflammatory diseases of the gastrointestinal tract: clinical conference, 58
- Klein, S., et al., Inflammatory diseases of the gastrointestinal tract: Clinical conference, 58
- L**ABORATORY in antibiotic therapy, The limitations of, (B. M. Wagner), 339
- Lear, H., A rapid method for determination of blood urea nitrogen, ^{ab}82
- Leavitt, D., et al., Blood exchange in replacement transfusions, studies with erythrocytes tagged with radioactive phosphorus, ^{ab}75
- Leiner, G. C., et al., The ineffectiveness of Khellin in the treatment of angina pectoris, 41
- Lester, L. J., et al., Megacolon, a complication of ulcerative colitis, ^{ab}83
- Levy, M. H., et al., The diagnostic significance of urinary pepsinogen excretion in diseases of the upper gastrointestinal tract, ^{ab}82
- Lichtman, P. A., et al., Penicillin prophylaxis of postoperative bacteremia and bacterial endocarditis, ^{ab}83
- Lidz, T., Emotional factors in the etiology and therapy of hyperthyroidism, 27
- Loevinger, R., et al., Clinical isodose curves, ^{ab}83
- Loevinger, R., Distribution of absorbed energy around a point source of beta radiation, ^{ab}77
- Lowry, E. L., et al., Collagen content of guinea pig tissues, ^{ab}73
- Lung, accessory, unusual variations, (G. P. Seley), 263
- Primary carcinoma of the, (A. H. Aufses), 212
- M**ANN, R., The capaciograph: An instrument for recording cardiac output, 360
- Margolin, H. N., et al., The use of radioactive gold in the treatment of effusions due to cancer, 237
- Margolin, S. G., Psychophysiological studies of fistulous openings into the gastrointestinal tract, 194

- Marshak, R., et al., Hysterography and hysterosalpingography, ^{ab77}
- Marshak, R. H., et al., Post-bulbar duodenal obstruction in carcinoma of the pancreas, ^{ab83}
- Value of hysterography in the diagnosis of large submucous uterine fibroids, ^{ab78}
- Master, A. M., et al., Penicillin prophylaxis of postoperative bacteremia and bacterial endocarditis, ^{ab83}
- Maxwell, M. H., et al., Measurement and significance of urinary appearance time in the dog, ^{ab78}
- Mayer, J. E., et al., The use of radioactive gold in the treatment of effusions due to cancer, 237
- Medical teaching mission to Israel and Iran, (L. M. Davidoff), 280
- Medicine, An integration of the psychosomatic viewpoint in, (M. R. Kaufman), 247
- Mednick, H., et al., Electrocardiographic studies of the normal cardiac cycle, ^{ab72}
- Megacolon, a complication of ulcerative colitis, (R. H. Marshak, et al.), ^{ab83}
- Megibow, S. J., et al., A method of automatic controlled respiration for anesthesia in the dog, ^{ab81}
- Megibow, S., et al., An experimental study of the cardiovascular effects of diodrast, ^{ab77}
- Melamed, S., et al., Some clinical experience in the use of Triethylene Melamine (T.E.M.), 16
- Meningitis, septic, with bacitracin, further experiences in treatment of, (P. Teng), ^{ab85}
- Metabolism of the human heart in vivo, (R. J. Bing), 100
- Metachronous carcinomas of the duodenum and the colon, (G. J. Lesnick), 140
- Metanephrogenic (retroperitoneal) cyst, Absence of right kidney, (G. D. Gordon and J. M. Silagy), 324
- Meyer, B. C., Should the patient know the truth?, 344
- Some gynecological implications of the castration complex, 267
- Minowitz, W., et al., Clinical isodose curves, ^{ab83}
- Morales, P. A., et al., Measurement and significance of urinary appearance time in the dog, ^{ab78}
- Moser, M., et al., Pheochromocytoma with calcification simulating cholelithiasis, ^{ab83}
- Mount Sinai Hospital, revelations from the early annual reports of the, (J. Hirsh), 151
- Multiple myeloma: lesions of the extraosseous hematopoietic system, (J. Churg and A. J. Gordon), ^{ab73}
- Mumps virus hemagglutination, role of the erythrocyte in inhibition by allantoic fluid of, (A. L. Florman), ^{ab73}
- Myasthenia gravis, studies in: edrophonium chloride (tensilon) test as a new approach to management, (K. E. Osserman, L. I. Kaplan, and G. Besson), 165
- NARINS, L., Congenital bilateral aplasia of the vas deferens, a factor in male sterility, ^{ab74}
- Nasal, a new splint, (I.B. Goldman), ^{ab82}
- Neo-fatty acids, (H. Sobotka and F. E. Styler), ^{ab79}
- OBESITY, Psychosomatic Aspects of, (H. Bruch), 1
- Oppenheimer, G. D., et al., Absence of right kidney: retroperitoneal (metanephrogenic) cyst, 324
- Orringer, D., Carcinoma of the stomach following surgery for chronic duodenal ulcer, ^{ab74}
- Osserman, K. E., et al., Studies in myasthenia gravis: Edrophonium chloride (tensilon) test as a New Approach to Management, 165
- Ostow, M., Clinical electroencephalography, ^{ab79}
- Psychodynamic disturbances in patients with temporal lobe disorder, 293
- Ostow, M., et al., The significance of bilateral abnormality in the electroencephalogram, 173
- PANCREAS, post-bulbar, obstruction in carcinoma of the pancreas (R. H. Marshak, et al.), ^{ab83}
- Pseudocyst of the, (A. Richman), 51
- Peck, S. M., The role of the antihistaminic drugs in producing cross-sensitization dermatitis, ^{ab78}
- Penicillin prophylaxis of postoperative bacteremia and bacterial endocarditis, (P. A. Lichtman and A. M. Master), ^{ab83}
- Pepsinogen excretion, urinary, the diagnostic significance of, in diseases of the upper gastro-intestinal tract, (H. D. Janowitz, M. H. Levy, and F. Hollander), ^{ab82}
- Pheochromocytoma with calcification simulating cholelithiasis, (M. Moser, G. Sheehan, and H. Schwinger), ^{ab83}
- Picrotoxin and amphetamine (benzedrine) sulfate in barbiturate intoxication, (B. W. Billow), ^{ab72}
- Pneumonia, primary atypical, an evaluation of aureomycin therapy in, (E. B. Schoenbach, et al.), ^{ab79}
- Polgar, N., et al., Dextrorotary acids of tubercle bacilli lipids, ^{ab72}
- Poliomyelitis infection, enhancing effect of cortisone upon, (G. Schwartzman), ^{ab84}
- Pregnancy, Diagnosis and treatment of afibrinogenemia in, (H. Chessin and J. C. Greenwald), 263
- Proctologic disorders, cod liver oil ointment therapy in, (R. Turell), ^{ab75}
- Pruritus vulvae due to aureomycin, (H. T. Behrman), ^{ab76}
- Pseudocyst of the pancreas, A. Richman, 51

- Psychodynamic disturbances in patients with temporal lobe disorder, (M. Ostow), 293
- Psychophysiological studies of fistulous openings into the gastrointestinal tract, (S. G. Margolin), 194
- Psychosomatic aspects of obesity, (H. Bruch), 1.
- viewpoint in medicine, an integration of the, (M. R. Kaufman), 247
- Public health, atherosclerosis, a problem in newer, (A. Keys), 118
- Pulmonary cyst, The development of an acquired, (H. J. Heimlich), 351
- R**ADIATION, beta, distribution of absorbed energy around a point source of, (R. Loevinger), ^{ab77}
- Radioactive Gold, in the treatment of effusions due to Cancer, (N. Simon, et al.), 237
- phosphorus, studies with erythrocytes tagged with, blood exchange in replacement transfusions, (L. R. Wasserman, et al.), ^{ab75}
- Rashkoff, I. A., et al., Blood exchange in replacement transfusions, studies with erythrocytes tagged with radioactive phosphorus, ^{ab75}
- Rectum and colon, adenomas of the, (R. Turell and R. S. Wilkinson), ^{ab75}
- Reports of the Mount Sinai Hospital, revelations from the early annual, (J. Ilirsch), 151
- Respiration, automatic controlled, for anesthesia in the dog, a method of, (M. H. Aelmlan, S. J. Megibow, and L. Blum), ^{ab81}
- Retroperitoneal (metanephrogenic) cyst, Absence of right kidney, (G. D. Oppenheimer and J. M. Silagy), 324
- Richman, A., Pseudocyst of the Pancreas, 51
- Root, W. S., The stimulus for erythropoiesis, 331
- Rosen, S., Fenestration by cold fracture method: preliminary report of an improved technique, ^{ab74}
- Teaching fenestration surgery, ^{ab78}
- Tympanomeatal membrane in the fenestration operation, (S. Rosen), ^{ab84}
- Rosenberg, S., et al., Films of hydrocarbon-stearic acid mixtures, ^{ab85}
- Films of omega-branched fatty acids, ^{ab85}
- Rosenfield, R. E., et al., Newer knowledge of human blood factors, 89
- S**AMET, P., et al., Electrocardiographic studies of the normal cardiac cycle, ^{ab72}
- Right-sided aortic arch, ^{ab84}
- Scalp, health and disease in the, (H. T. Behrman), 236
- Schendel, J. B., et al., Electrocardiographic studies of the normal cardiac cycle, ^{ab72}
- Schlesinger, B., Mental changes in intracranial tumors and related problems, ^{ab80}
- Schneerson, S. S., et al., Problems in the treatment of refractory bacterial infections, 285
- The importance of the laboratory in antibiotic therapy, 155
- Schoenbach, E. B., et al., An evaluation of aureomycin therapy in primary atypical pneumonia, ^{ab79}
- Schwinger, H., et al., Pheochromocytoma with calcification simulating cholelithiasis, ^{ab83}
- Sedimentation differential agglutination test, (D. Stats), ^{ab75}
- Seley, G. P., Accessory lung—unusual variations, 263
- Seley, G. P., et al., Bilateral temporomandibular ankylosis, 145
- Selye, H., Annual report on stress, ^{ab87}
- Sharney, L., et al., Blood exchange in replacement transfusions, studies with erythrocytes tagged with radioactive phosphorus, ^{ab75}
- Blood exchange in replacement transfusions, theoretic considerations, ^{ab75}
- Sheehan, G., et al., Pheochromocytoma with calcification simulating cholelithiasis, ^{ab83}
- Should the patient know the truth?, (B. C. Meyer), 344
- Shwartzman, G., Enhancing effect of cortisone upon poliomyelitis infection, ^{ab84}
- Suppression of the phenomenon of local tissue reactivity by ACTH, cortisone and sodium salicylate, ^{ab74}
- Silagy, J. M., et al., Absence of right kidney: retroperitoneal (metanephrogenic) cyst, 324
- Silbert, S., et al., Results of midleg amputations for gangrene in diabetics, ^{ab74}
- Silver, S., et al., Blood levels of I-131 after tracer doses in the diagnosis of hyperthyroidism, ^{ab79}
- Simon, N., et al., The use of radioactive gold in the treatment of effusions due to cancer, 237
- Sobotka, H., et al., Films of hydrocarbon-stearic acid mixtures, ^{ab85}
- Films of omega-branched fatty acids, ^{ab85}
- Neo-fatty acids, ^{ab79}
- Shortening of bleeding time by a water-soluble adrenochrome derivative, ^{ab84}
- Sodium salicylate, ACTH and cortisone, suppression of the phenomenon of local tissue reactivity by, (G. Shwartzman), ^{ab74}
- Stats, D., Sedimentation differential agglutination test, ^{ab75}
- Steinberg, M. R., Six principles of purchasing for the equipment of new and remodeled areas, ^{ab75}
- Sterility, a factor in male, congenital bilateral aplasia of the vas deferens, (L. Narins), ^{ab74}
- Stern, Jr., L., et al., Bilateral temporomandibular ankylosis, 145
- Sternstein, M., et al., Inflammatory diseases of the gastrointestinal tract: clinical conference, 58
- Stomach, carcinoma of the, following surgery for chronic duodenal ulcer, (D. Oringer), ^{ab74}
- differentiation from carcinoma of the:

- Localized hypertrophied gastric folds, (S. I. Gurman and B. S. Wolf), 315
- Stone, D. J., et al., Right-sided aortic arch, ^{ab}84
- Strauss, H., et al., Correlation of clinical and EEG abnormalities in tumors and vascular disease of the brain, ^{ab}86
- The significance of bilateral abnormality in the electroencephalogram, 173
- Stress, annual report on, (H. Selye), ^{ab}87
- Stynler, F. E., et al., Neo-fatty acids, ^{ab}79
- Sussman, M. L., et al., An experimental study of the cardiovascular effects of diodrast, ^{ab}77
- Swed, A., et al., An evaluation of aureomycin therapy in primary atypical pneumonia, ^{ab}79
- T**EMPORAL lobe disorder, Psychodynamic disturbances in patients with, (M. Ostow), 293
- Temporomandibular ankylosis, bilateral, (G. P. Seley, et al.), 145
- Teng, P., Further experiences in treatment of septic meningitis with bacitracin, ^{ab}85
- Teng, P., et al., The effect of intraneural injection of bacitracin in rabbits, 46
- Tensilon (edrophonium chloride) test as a new approach to management, Studies in myasthenia gravis, (K. E. Osserman, L. I. Kaplan, and G. Besson), 165
- Tension, the therapeutic management of group, (W. C. Hulse), ^{ab}73
- Tepper, B., et al., An evaluation of aureomycin therapy in primary atypical pneumonia, ^{ab}79
- Therapy, antibiotic, the importance of the laboratory in, (S. S. Schneerson and M. S. Bryer), 155
- antibiotic, the limitations of the laboratory in, (B. M. Wagner), 339
- Transfusions, replacement, blood exchange in, studies with erythrocytes tagged with radioactive phosphorus, (L. R. Wasserman, et al.), ^{ab}75
- replacement, blood exchange in, theoretic considerations, (L. R. Wasserman and L. Sharney), ^{ab}75
- Treatment of angina pectoris, The ineffectiveness of Khellin in, (G. C. Leiner and S. Dack), 41
- Triethylene Melamine (T.E.M.), some clinical experience in the use of, (D. J. Hammerman and S. Melamed), 16
- Tubercle bacilli lipids, dextrorotary acids of, (J. D. Chanley and N. Polgar), ^{ab}72
- Tumor, Granulosa cell, (A. Bellwin and M. A. Goldberger), 229
- Tumors and vascular disease of the brain, correlation of clinical and EEG abnormalities in, (E. A. Weinstein, R. L. Kahn and H. Strauss), ^{ab}86
- intracranial, and related problems, mental changes in, (B. Schlesinger), ^{ab}80
- Turell, R., et al., Adenomas of the colon and rectum, ^{ab}75
- An evaluation of present day surgical procedures in diseases of the lower bowel, ^{ab}85
- Turell, R., Cod liver oil ointment therapy in proctologic disorders, ^{ab}75
- U**LCKER, chronic duodenal, carcinoma of the stomach following surgery for, (D. Orringer), ^{ab}74
- peptic, of the esophagus, partial resection for, (A. Cornell and A. Winkelstein), ^{ab}82
- Urinary appearance time in the dog, measurement and significance of, (P. A. Morales, C. H. Crowder, A. P. Fishman, M. H. Maxwell, and D. M. Gomez), ^{ab}78
- V**AS Deferens, congenital aplasia of the, a factor in male sterility, (L. Narins), ^{ab}74
- Vertebra, longitudinal growth of the human, (E. M. Bick), ^{ab}72
- Viral infections, An introduction to the pathogenesis of, (A. L. Florman), 309
- Vivo, the metabolism of the human heart in, (R. J. Bing), 100
- Vogel, P., et al., newer knowledge of human blood factors, 89
- W**AGNER, B. M., The limitations of the laboratory in Antibiotic Therapy, 339
- Wasserman, L. R., et al., Blood exchange in replacement transfusions, studies with erythrocytes tagged with radioactive phosphorus, ^{ab}75
- Blood exchange in replacement transfusions, theoretic considerations, ^{ab}75
- Webster, J. J., Adrenal cortex in liver disease, ^{ab}76
- Weinstein, E. A., et al., The syndrome of anosognosia, ^{ab}86
- Correlation of clinical and EEG abnormalities in tumors and vascular disease of the brain, ^{ab}86
- Wilder, R. J., Failure of repeated intraperitoneal injection of hyaluronidase to prevent recurrence of abdominal adhesions in rats, 278
- Wilkinson, R. S., Adenomas of the colon and rectum, ^{ab}75
- Wilkinson, R. S., et al., An evaluation of present day surgical procedures in diseases of the lower bowel, ^{ab}85
- Winkelstein, A., et al., Inflammatory diseases of the gastrointestinal tract: Clinical conference, 58
- Partial gastric resection for peptic ulcer of the esophagus, ^{ab}82
- Wolf, B. S., et al., Clinical isodose curves, ^{ab}83
- Localized hypertrophied gastric folds: differentiation from carcinoma of the stomach, 315
- Y**OH, Tse-Fei, et al., Blood exchange in replacement transfusions, studies with erythrocytes tagged with radioactive phosphorus, ^{ab}75



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